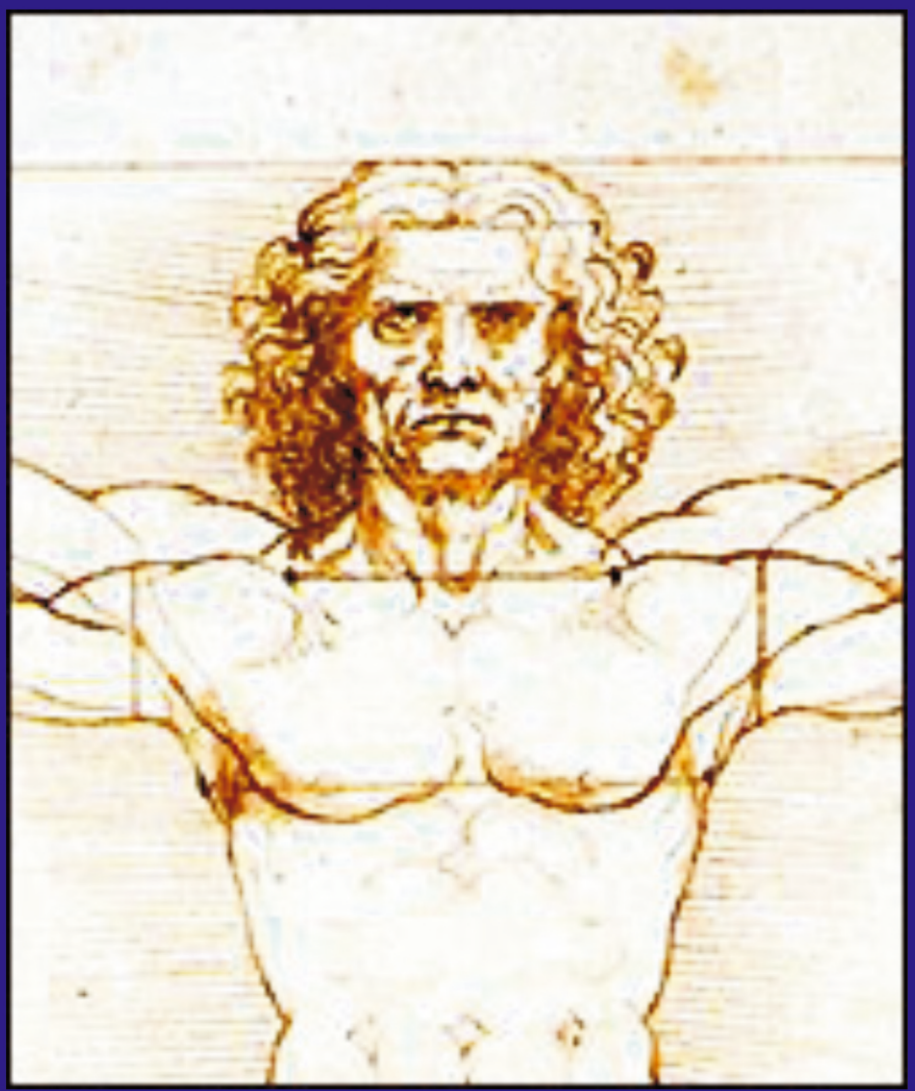
SANAMED

ISSN-1452-662X



Vol 20 (3) 2025.

MEDICAL JOURNAL

ISSN-1452-662X

IZDAVAČ
Udruženje lekara Sanamed, Novi Pazar

ČASOPIS IZLAZI TRI PUTA GODIŠNJE

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

ŠTAMPA
„OFSET“, Kraljevo

TIRAŽ
500

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

ISSN-1452-662X

PUBLISHER
Association ofmedical doctors “Sanamed”, Novi Pazar

ISSUED THREE TIMES A YEAR

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

PRINT
“OFSET”, Kraljevo

CIRCULATION
500

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

SANAMED

ISSN-1452-662X

Recenzenti / Reviewers

Aleksandar Karamarković (Serbia)
Radivoj Kocić (Serbia)
Stojan Sekulić (Serbia)
Miloš Jovanović (Serbia)
Branka Nikolić (Serbia)
Nermina Babić (Bosnia and Herzegovina)
Miralem Musić (Bosnia and Herzegovina)
Nermina Hadžigrahić (Bosnia and Herzegovina)
Maja Abram (Croatia)
Goran Spasojević (Bosnia and Herzegovina)
Ljubica Živić (Serbia)
Hasan Žutić (Bosnia and Herzegovina)
Slobodan Milisavljević (Serbia)
Zoran Todorović (Serbia)
Lepša Zorić (Serbia)
Ivan Dobrić (Croatia)
Jovan Mladenović (Serbia)
Sergio Zylbersztejn (Brazil)
Spase Jovkovski (N. Macedonia)
Dejan Petrović (Serbia)
Samir Delibegović (Bosnia and Herzegovina)
Naima Arslanagić (Bosnia and Herzegovina)
Gordana Petručevska (N. Macedonia)
Todorović Vladimir (Montenegro)
Miodrag V. Šoć (Montenegro)
Eugen Carasevici (Romania)
Kostandina L. Korneti-Pekevska (N. Macedonia)
Snežana Lazić (Serbia)
Sanja Milenković (Serbia)
Slavica Vujisić (Montenegro)
Vasileios K. Nitsas (Greece)
Miroslava Gojnić Dugalić (Serbia)
Tatjana Đurđević Mirković (Serbia)
Radmila Gudović (Serbia)
Čedomir Dimitrovski (N. Macedonia)
Katarina Vukojević (Croatia)
Svetoslav Kalevski (Bulgaria)
Milos Tatar (Slovakia)
Ludek Vajner (Czech Republic)
Miroslav Votava (Czech Republic)
Izet Hozo (Croatia)
Ljiljana Kesić (Serbia)
Alexander Rapoport (Latvia)
Dejan Vulović (Serbia)
Sunčica Srećković (Serbia)
Slobodanka Đukić (Serbia)
Fahrija Skokić (Bosnia and Herzegovina)
Suzana Pavljašević (Bosnia and Herzegovina)
Milovan Matović (Serbia)
Zsolt Molnar (Hungary)
Emir Tupković (Bosnia and Herzegovina)
Peter Laszlo Kanizsai (Hungary)
Janko Kersnik (Slovenia)
Fatima Numanović (Bosnia and Herzegovina)
Božena Pejković (Slovenia)
Ervin Alibegović (Bosnia and Herzegovina)
Željko Mijailović (Serbia)
Vesna Koželj (Slovenia)
Mirko Omejc (Slovenia)
Karmen Lončarek (Croatia)
Mina Cvjetković Bošnjak (Serbia)
Branko Kolarić (Croatia)
Andrej Čretnik (Slovenia)
Iztok Takač (Slovenia)
Mirjana Bećarević (Serbia)
Kenan Arnautović (USA)
Biljana Antonijević (Serbia)
Milkica Nešić (Serbia)
Vesna Matović (Serbia)
Irena Hočevar-Boltežar (Slovenia)
Ivica Mažuranić (Croatia)
Darko Kaštelan (Croatia)
Grozdanko Grbeša (Serbia)
Enes M. Kanlić (USA)
Branislav Baškot (Serbia)
Ivan Kopitović (Serbia)
Vjekoslav Gerc (Bosnia and Herzegovina)
Nihada Ahmetović (Bosnia and Herzegovina)
Jasna Huremović (Bosnia and Herzegovina)
Risto Kozomara (Bosnia and Herzegovina)
Mevludin Mekić (Bosnia and Herzegovina)
Elvira Konjić (Bosnia and Herzegovina)

Darko Zdravkovic (Serbia)
Gordana Kamceva Mihailova (N. Macedonia)
Nevenka Velickova (N. Macedonia)
Dance Vasileva (N. Macedonia)
Jasmina Golaboska (N. Macedonia)
Vojislav Cupurdija (Serbia)
Biljana Ljujic (Serbia)
Milos Velinovic (Serbia)
Demet Sengul (Turkey)
Mehmet Kutalay (USA)
Katarina Janicijevic (Serbia)
Marina Roksandic Milenkovic (Serbia)
Brihaspati Sigdel (Nepal)
Andrea Piccin (Ireland)
Nesad Hotic (Bosnia and Herzegovina)
Abduaal Mohamed Saied (Sudan)
Maja Sazdanovic (Serbia)
Verica Misanovic (Bosnia and Herzegovina)
Belkisa Colic-Hadzic (Bosnia and Herzegovina)
Predrag Stilet (Montenegro)
Marko Folic (Serbia)
Juan Manuel Rodrigez-Tafur Davila (Peru)
Jasmina Katanic, Serbia
Dragan Nikolic, Serbia
Irmina Sefic Pašić, BH
Milena Djurovic, Montenegro
Antoaneta Adžic, Montenegro
Dalibor Stajic, Serbia
Snežana Radovanovic, Serbia
Ivana Simic Vukomanovic, Serbia
Fatih Guzelbulut, Turkey
Muharrem Keskin, Turkey
Hakan Yıldız, Turkey
Necmiye Tijen Yesim, Turkey
Zuhal Saglam, Turkey
Idris Kuzu,Turkey
Ayşe Gonca Kaçar, Turkey
Emine Türkkan, Turkey
Merve Boşat, Turkey
Eray Yurtseven, Turkey
Cemile Nihal Yurtseven, Turkey
Vesna Ecim, Serbia
Snezana Crnogorac, Serbia
Emina Kiseljakovic, BH
Zafer Bıcakcı, Turkey
Halil Keskin, Turkey
Nemanja Milincic, Serbia
Maja Malenica, BH
Emina Colic, BH
Gönül Acar, Turkey
Dilek Yalnızoğlu, Turkey
Predrag Jovanovic, Serbia

Aleksandar Miljković, Serbia
Darinka Glamuzina, BH
Füsun Mayda Domaç, Turkey
Aynur Ozge, Turkey
Sadan Hacısalihoglu, Turkey
Sehnaz Ulasan, Turkey
Nada Santrac, Serbia
İlker Ödemiş, Turkey
Arzu Nazlı, Turkey
Sadeta Hamzic, BH
Sabina Sestic, BH
Miljan Ceranic, Serbia
Nikola Grubor, Serbia
Zoran Damnjanović, Serbia
Natasa Rančić, Serbia
Lidija Savic, Serbia
Dragan Matic, Serbia
Dejan Aleksic, Serbia
Olivera Pilipović Spasojević, BH
Marko Buta, Serbia
Ana Bosak Versic, Croatia
Emina Ejubovic, BH
Tatjana Roganović, BH
Harun Avdagic, BH
Milos Stevic, Serbia
Amila Mehmedovic, BH
Marko Baralic, Serbia
Igor A. Kryvoruchko, Ukraine
Damir Celik, BH
Dusica Stamenkovic, Serbia
Martin Popević, Serbia
Milena Vesković, Serbia
Sanela Slavkovic, Serbia
Sanja Milutinovic Smiljanic, Serbia
Ekaterina Gubareva, Russia
Snežana Pantović, Montenegro
Andrija Jovic, Serbia
Vladan Bošković, Montenegro
Ghada Elgohary, Egypt
Igor Sekulic, Serbia
Aneta Sima, N. Macedonia
Dragana Bozic, Serbia
Ivana Likic, Serbia
Ljiljana Lukic, Serbia
Sanja Vujkov, Serbia
Ivana Gušić, Serbia
Semir Mesanovic, BH
Dragan Milosevic, BH
Morena Milic, Croatia
Sanita Maleškić Kapo, BH
Rudin Domi, Albania
Ammad Ahmed, BH

SANAMED

Number 20(3)/2025

CONTENT

SANAMED

Number 20(3)/2025

SADRŽAJ

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

* * *

Read to understand

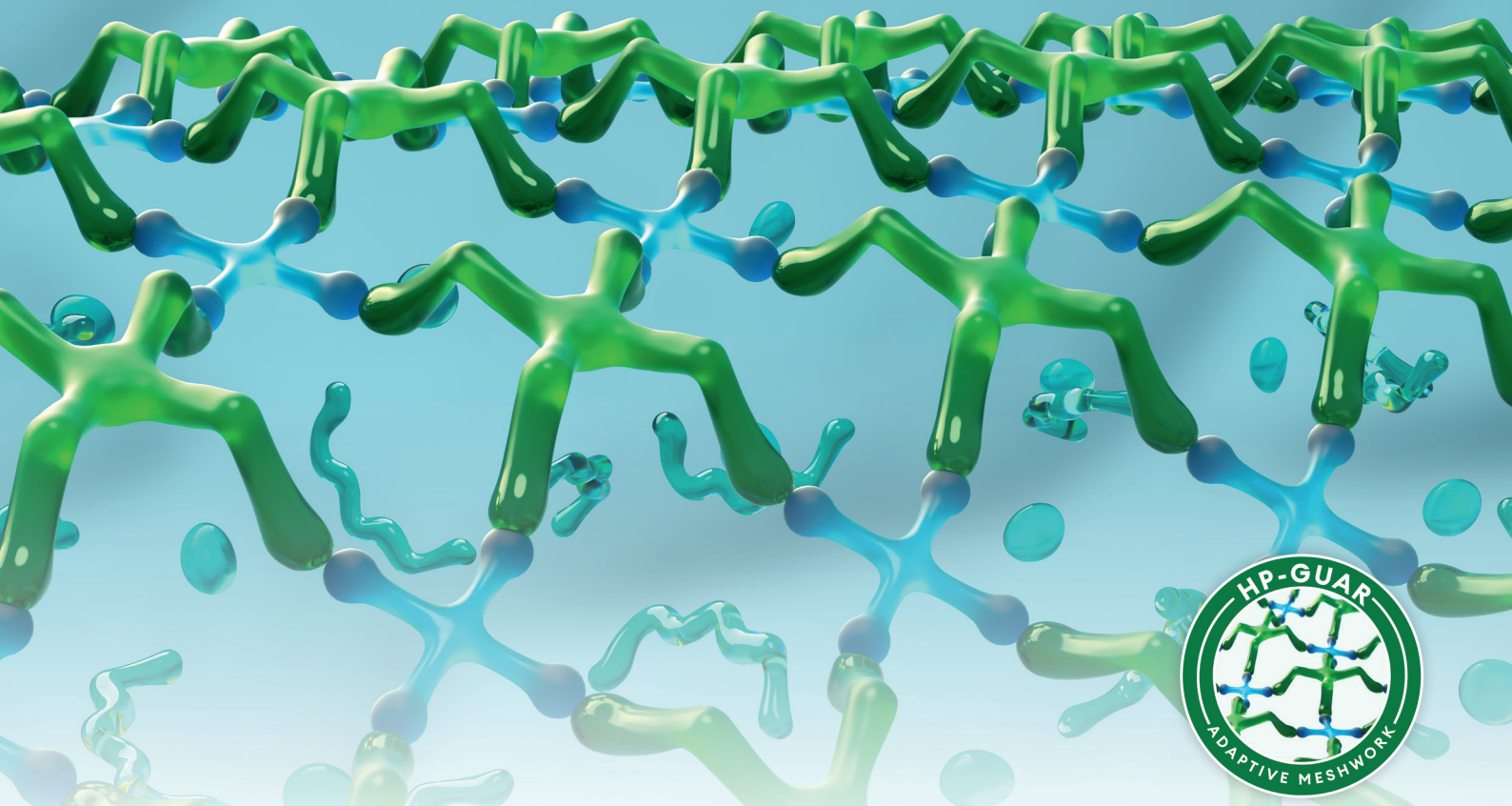
Write to impart

Work to be remembered

Avdo Ćeranić

Systane®

kapi za vlaženje oka



EL PHARMA
a PHOENIX company

Ovlašćeni predstavnik proizvođača: Evropa Lek Pharma d.o.o. Bore Stankovića 2, Beograd

SANAMED
2025; 20(3): 241–242
ISSN-1452-662X

DOI: 10.5937/sanamed0-62870
UDK: 577.113.8
ID: 183828745
Letter to the Editor

REASSESING RIBONUCLEIC ACID ISOLATION FROM HUMAN MONONUCLEAR CELL CULTURE WITH MAGNETIC BEADS PRE-ENRICHMENT FOR MOLECULAR ANALYSIS

Sengul Ilker[1, 2, 3] Sengul Demet[4]

[1] Giresun University Faculty of Medicine, Thyroidology Unit, TR-28100 Giresun, Turkey
[2] Giresun University Faculty of Medicine, Division of Endocrine Surgery, TR-28100 Giresun, Turkey
[3] Giresun University Faculty of Medicine, Department of General Surgery, TR-28100 Giresun, Turkey
[4] Giresun University Faculty of Medicine, Department of Pathology, TR-28100 Giresun, Turkey

Primljen/Received: 18. 11. 2025. Prihvaćen/Accepted: 13. 12. 2025. Online First: 23. 12. 2025.

Dear Editor,

It is with considerable interest that I have perused the recently published contribution by Bhatia, entitled *"Ribonucleic Acid Isolation from Human Mononuclear Cell Culture with Magnetic Beads Pre-enrichment for Molecular Analysis,"* set forth within *Sanamed*, volume 19(1). The author addresses a conundrum of pronounced import for those engaged in molecular analyses and the development of immunotherapies. As such, the established difficulty of extracting ribonucleic acid (RNA), particularly from mononuclear cell (MNC) cultures exceeding a few months in age, is well documented within the author's own laboratory experience, having persisted, as stated, for over two years of consistent failure.

The developed methodology, centered upon the pre-enrichment of the cultured MNCs utilizing Cluster of Differentiation 45 (CD45)-specific magnetic beads antecedent to the customary mini column isolation, proves efficacious where previous attempts faltered. The successful isolation of RNA from cultures exceeding six months in duration—confirmed through spectrophotometric yield measurements and subsequent conventional and real-time Polymerase Chain Reaction (PCR) assays for the beta-actin housekeeping gene—is indeed a notable technical advancement. The assertion that this study constitutes the inaugural demonstration of isolating RNA from aged human MNC cultures via specific magnetic beads is, moreover, a claim that warrants careful consideration.

Notwithstanding the demonstrated success of this technique, one might cast an inquiring gaze upon certain aspects of the execution and presentation. Firstly, the affiliation of the esteemed author with Genekam Biotechnology AG, which entity serves as the sole source for the crucial magnetic beads, the mini column isolation kit, the PCR kits, and the specialized magnetic rack, invites circumspection. Whilst proprietary methods often feature in novel protocols, the near-total reliance upon reagents and apparatus supplied by the author's own commercial interest renders the protocol less immediately accessible or generalizable for laboratories not possessed of the aforementioned instruments and supplies. The efficacy of the method, therefore, appears for the present to be closely associated with this particular commercial supply chain.

Secondly, whilst the author reports that the initial method failed consistently over two years, and that isolation without magnetic beads was not achieved, the results presented lack detailed quantitative metrics comparing the failed isolations to the successes. The presentation of "failure" in Table 1 illustrates the necessity of the pre-enrichment step, yet does not afford the readership an optimal means to gauge the precise extent of nucleic acid degradation or inhibition encountered previously—data which would further illuminate the magnitude of the technical challenge overcome.

Finally, the discussion alludes to further consequential applications of the isolated RNA—namely, its conversion to complementary DNA (cDNA) and subsequent use for other purposes—yet these vital data are deferred for "future publications." Herewith, a more comprehensive elucidation of the robustness of the isolated material might have been advantageously reserved for this singular publication, ensuring that the full scope of the methodology's utility is presented forthwith (1).

In essence, whilst the developed magnetic bead pre-enrichment methodology provides a much-needed solution for obtaining RNA from refractory MNC cultures, it is sincerely hoped that future work will include more extensive comparative data and endeavor to ascertain the protocol's viability utilizing reagents sourced from diverse suppliers, thereby further affirming its widespread applicability in molecular diagnostics and therapeutic development. This issue merits further investigation. We thank Bhatia et al. (1) for their valuable study on RNA isolation from human MNC culture with molecular analysis.

Abbreviations

MNC – Mononuclear Cells
CD45 – Cluster of Differentiation 45
PCR – Polymerase Chain Reaction
RNA – Ribonucleic Acid
cDNA – Complementary DNA

Funding: No funding was available.

Conflicts of Interest: None declared.

Author Contribution & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. **Authors' contributions**: **IS**: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; **DS**: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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

REFERENCES

1. Bhatia S. Ribonucleic Acid Isolation from Human Mononuclear Cell Culture with Magnetic Beads Pre-enrichment for Molecular Analysis. Sanamed. 2025;19(3):275–9. doi: 110.5937/sanamed0-50158.

Correspondence to/Autor za korespondenciju
Prof. Demet Sengul, M.D.
Editor-in-Chief „*Sanamed*" journal, Serbia
Founder & Chair, Department of Pathology
Founder, Scientific and Research Laboratories
Giresun University Faculty of Medicine
TR-28100, Giresun, Turkey
email: demet.sengul.52@gmail.com
WoS: A-3035-2019; Scopus: 22938589200
ORCID numbers
Sengul Demet 0000-0002-0416-0621
Sengul Ilker 0000-0001-5217-0755

***How to cite this article**:* **Sengul I, Sengul D.** Reassessing Ribonucleic Acid Isolation from Human Mononuclear Cell Culture with Magnetic Beads Pre-enrichment for Molecular Analysis. Sanamed. 2025; 20(3): 241-242. doi: 10.5937/sanamed0-62870.

SANAMED
2025; 20(3): 243–249
ISSN-1452-662X

DOI: DOI: 10.5937/sanamed0-61135
UDK: 618.5-089.888.61-06:616-007.43(532)"2023/2025"
ID: 183829513
Original article

RISK FACTOR STRATIFICATION AND EARLY DETECTION OF INCISIONAL HERNIAS AFTER CESAREAN AND OPEN GYNECOLOGIC PROCEDURES: A PROSPECTIVE OBSERVATIONAL STUDY

Memon Munir Muhammad,[1, 2] Salati Ahmad Sajad,[3] Saadia Zaheera[4]

[1] Qassim University Buraidah branch, College of Medicine, Department of Surgery, Kingdom of Saudi Arabia
[2] Bin Tayyab Medical Complex (BTMC), Hyderabad, Sindh, Pakistan
[3] Qassim University, Unayzah branch, College of medicine, Department of Surgery, Kingdom of Saudi Arabia
[4] Qassim University, Buraidah branch, College of Medicine, Department of Gynecology, Kingdom of Saudi Arabia

Primljen/Received: 28. 08. 2025. Prihvaćen/Accepted: 26. 10. 2025. Online First: 31. 10. 2025.

Abstract: **Background:** Incisional hernia is a major complication of abdominal surgery, leading to pain, functional impairment, and increased healthcare costs. This study aimed to identify and rank risk factors for incisional hernia in patients undergoing Cesarean section or open gynecologic surgery, and to evaluate strategies for early detection.

Methods: From January 2023 to June 2025, a prospective observational study enrolled 200 women, each followed for 12 months. Half of the women underwent Cesarean section (n = 100) and the other half underwent open gynecologic surgery (n = 100). Data were collected on patient demographics, body mass index, comorbidities, surgical details, and complications. The primary outcome was the incidence of incisional hernia within one year, assessed by clinical examinations at 6 weeks, 6 months, and 12 months.

Results: The overall incidence of incisional hernia was 8.0% (16/200), with 6.0% (6/100) after Cesarean section and 10.0% (10/100) after open gynecologic procedures. Multivariable analysis identified independent risk factors: higher body mass index (adjusted odds ratio 1.12 per unit, 95% confidence interval 1.05–1.19, $p < 0.001$), vertical incision (odds ratio 4.10, 95% CI 1.75–9.60, $p = 0.001$), postoperative wound infection (odds ratio 5.22, 95% CI 2.15–12.67, $p < 0.001$), and history of two or more prior Cesarean sections (odds ratio 3.85, 95% CI 1.42–10.45, $p = 0.008$). Continuous fascial closure was protective (odds ratio 0.42, 95% CI 0.20–0.88, $p = 0.022$). Early patient-reported symptoms preceding diagnosis included a palpable bulge (75%), persistent pain (62.5%), and discomfort during activity (50%).

Conclusion: Higher body mass index, vertical incisions, wound infection, and multiple prior Cesarean sections are significant risk factors for incisional hernia. Using transverse incisions and continuous fascial closure, when possible, together with vigilant wound care and patient education on self-examination for early symptoms, can help reduce risk and enable early detection in high-risk patients.

Keywords: Incisional hernia, Cesarean section, gynecologic surgery, risk factors, prospective study, obesity, surgical site infection.

INTRODUCTION

An incisional hernia (IH) is a common adverse outcome of abdominal surgery that can result in substantial morbidity (1) and increased medical expenses (2). Research indicates a strong correlation between the number of Cesarean sections (CSs) performed on a patient and the subsequent risk of incisional hernia (IH) (3). Reported incidence rates of IH after CS vary widely. Paulsen et al. (4), in a systematic analysis of five studies comprising 275,878 women with a previous CS, reported an occurrence of IH after CS between 0.0% and 5.6%, with follow-up periods ranging from six months to ten years.

Incisional hernia repair operations are often used as a proxy for the true incidence of IH, which likely underestimates the total number of clinically significant cases. In one cohort where transverse incisions were the primary approach, the overall probability of an IH necessitating surgical repair within ten years following CS was 2 per 1000 deliveries (5).

The incidence of IH following gynecological surgeries has been reported to range from 2% to 17%, with risk variables comparable to those observed in gastrointestinal surgery (6). Gynecological operations

have been recognized as an independent risk factor for IH (6,7). Studies indicate that the overall incidence of IH after off-midline and Pfannenstiel incisions is typically much lower than after midline laparotomy. Although Pfannenstiel incisions are often used for procedures such as CS, they may be inadequate for gynecological oncology procedures requiring wider surgical exposure (8).

Other established patient-related risk factors include obesity, diabetes, and advanced age, while surgical risk factors encompass vertical midline incisions, suture technique, postoperative surgical site infection (SSI), history of multiple CSs, and postoperative behaviors such as sedentary lifestyle.

Despite this knowledge, prospective data specifically stratifying risk factors and the natural history of IH in these common surgical populations remain limited. This study prospectively evaluated risk factors, symptomatology, and timing of IH after CS and open gynecologic surgery, with the goal of informing risk-stratified prevention and surveillance strategies.

PATIENTS AND METHODS

Research design and participants

A prospective observational cohort study was conducted from January 2023 to June 2025 at the Departments of General Surgery and Obstetrics & Gynecology at Bin Tayyab Medical Complex (BTMC), Hyderabad, Pakistan. Consecutive women scheduled for elective or emergency Cesarean section (CS; n = 100) or open gynecologic procedures (n = 100) via Pfannenstiel or midline incision were recruited. Exclusion criteria included pre-existing abdominal wall hernias, prior hernia repair surgery, inability to provide informed consent, or plans to relocate that would prevent follow-up. The study received ethical approval from the BTMC Institutional Review Board, and all participants provided written informed consent.

Data Collection

Baseline data collected preoperatively included:

• **Demographics:** Age, parity.

• **Anthropometrics:** Height and weight were measured to calculate Body Mass Index (BMI).

• **Medical History:** Comorbidities (hypertension, diabetes mellitus), smoking status, and history of prior abdominal surgeries, with specific notation of the number of previous Cesarean sections (CS).

• **Surgical Details:** Type of incision (Pfannenstiel vs. midline) and fascial closure technique (continuous vs. interrupted).

Patients were followed up at 6 weeks, 6 months, and 12 months through scheduled clinic visits. At each visit, a surgeon performed a physical examination to assess for an IH, diagnosed as a palpable defect or bulge at the surgical site. Patients were also interviewed using a structured questionnaire regarding symptoms, including persistent pain (rated on a visual analog scale), sensation of a bulge, discomfort during physical activity, or a feeling of pressure.

The occurrence of postoperative wound infection, defined according to CDC criteria and requiring antibiotic treatment or intervention, was recorded. Physical activity levels were self-reported and classified into three categories: low (< 30 minutes of moderate activity per week), moderate (30–150 minutes per week), and high (> 150 minutes per week).

Clinical Endpoint

The primary outcome was the incidence of a clinically detectable incisional hernia (IH) within 12 months post-surgery.

Secondary outcomes included:

1. Time from surgery to hernia detection.
2. Identification of independent risk factors for IH development.
3. Analysis of initial symptoms reported before diagnosis.

Statistical Analysis

All data were analyzed using SPSS version 27.0. Continuous data with normal distribution are presented as means ± standard deviations, while skewed continuous data are expressed as medians with interquartile ranges. Categorical variables are reported as frequencies and percentages.

Comparisons between groups were performed using the independent-samples t-test, Mann–Whitney U test, or Chi-square test, as appropriate. To identify potential risk factors, univariate logistic regression was first used ($p < 0.10$ threshold). Variables meeting this criterion were entered into a multivariable logistic regression model using a backward stepwise approach to determine independent predictors. Results are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant.

RESULTS

Participant characteristics at enrollment

Table 1 summarizes the baseline characteristics of the 200 study participants. On average, participants were 34.2 years old (± 6.5 years) with a mean BMI of 28.5 kg/m² (± 4.2 kg/m²). In the Cesarean section (CS) group, the median number of prior deliveries was 1,

Table 1. *Descriptive statistics of the study population*

Characteristic	Overall (n = 200)	Cesarean Section (n = 100)	Open Gynecologic (n = 100)	p-value
Age (years), mean ± SD	34.2 ± 6.5	32.8 ± 5.9	35.6 ± 6.8	0.003
BMI (kg/m²), mean ± SD	28.5 ± 4.2	29.1 ± 4.5	27.9 ± 3.9	0.038
Parity, median [IQR]	2 [1, 3]	2 [1, 3]	–	–
≥ 2 Prior Cesareans, n (%)	45 (22.5)	45 (45.0)	–	–
Incision Type, n (%)				< 0.001
Pfannenstiel	100 (50.0)	85 (85.0)	15 (15.0)	
Midline	100 (50.0)	15 (15.0)	85 (85.0)	
Closure Technique, n (%)				1.000
Continuous	160 (80.0)	80 (80.0)	80 (80.0)	
Interrupted	40 (20.0)	20 (20.0)	20 (20.0)	
Comorbidities, n (%)				
Diabetes Mellitus	10 (5.0)	5 (5.0)	5 (5.0)	1.000
Hypertension	20 (10.0)	8 (8.0)	12 (12.0)	0.343
Postoperative Wound Infection, n (%)	25 (12.5)	10 (10.0)	15 (15.0)	0.278

with an interquartile range of 1 to 2, indicating that the middle 50% of values fell between 1 and 2.

The median time to hernia detection in our study was 5.5 months (interquartile range [IQR]: 3–9 months). Open gynecologic procedures included hysterectomy (65%), myomectomy (25%), and oophorectomy (10%). The use of midline incisions was significantly higher in the open surgery group, occurring in 70% of cases, whereas it was less common in the CS group (15%), where Pfannenstiel incisions predominated (85%). Continuous fascial closure was used in 80% of all procedures.

Incidence and Time to Detection

The overall incidence of incisional hernia at 12 months was 8.0% (16/200). The incidence was 6.0% (6/100) following Cesarean section (CS) and 10.0% (10/100) after open gynecologic procedures. The average time to hernia detection was 6 months, with most detections occurring between 4 and 8 months.

A Kaplan-Meier curve illustrating cumulative incidence over time is presented in Figure 1. In Figure 2, the median time to hernia detection after open gynecologic operations is shown at 5.6 months by a line within the box, which spans an interquartile range (IQR) of 4–8 months (Q1 = 4 months, Q3 = 8 months). Figure 2 clearly illustrates the spread and central tendency of the data. In contrast, the IQR for the CS group (1–2 months) is shown as a smaller, tighter box, representing a narrow spread of data.

Thus, Figure 1 shows the approximate hernia-free survival over 12 months for CS and open gynecologic surgery patients, whereas Figure 2 visualizes the distribution of time to hernia detection (IQR 4–8 months) for each group, including individual patient events.

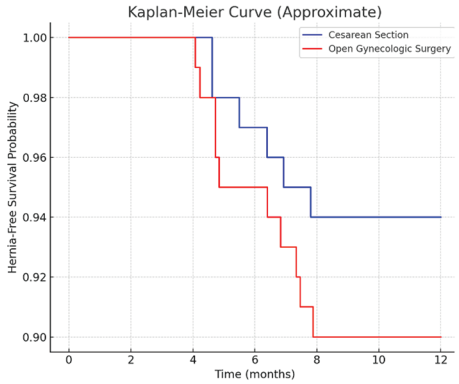


Figure 1. *Kaplan–Meier curve showing the cumulative incidence of incisional hernia over 12 months postoperatively, comparing Cesarean section and open gynecologic surgery patients. The x-axis represents time in months, and the y-axis represents the cumulative probability of hernia occurrence*

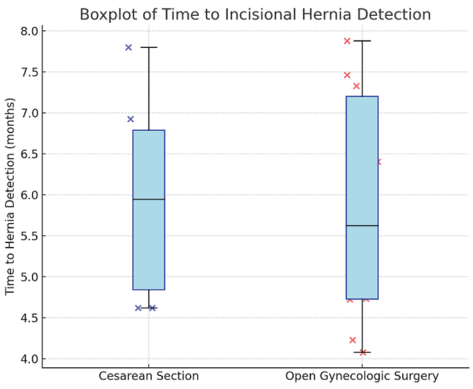


Figure 2. *Box-and-whisker plot showing the time to incisional hernia detection among patients diagnosed with IH (n = 16). The median is indicated by the line within the box, the interquartile range (IQR) by the box, and the whiskers represent the minimum and maximum values*

Risk Factor Analysis

Univariate analysis identified higher BMI, vertical incision, postoperative wound infection, and a history of two or more prior Cesarean sections as significant factors associated with IH development (Table 2).

DISCUSSION

This prospective observational study provides robust evidence for risk stratification of incisional hernias (IH) following common gynecological and obstetric surgeries. Our findings confirm and quantify several established risk factors while highlighting the cumulative risk posed by multiple prior Cesarean sections. The overall IH incidence of 8.0% aligns with the higher end of the range reported in contemporary literature for mixed surgical cohorts, reflecting our prospective design, which may capture hernias that retrospective studies miss (4, 6, 9).

Table 2. *An analysis of the unadjusted association between variables and the development of incisional hernia*

Variable	No Hernia (n = 184)	Hernia (n = 16)	O R (95% CI)	p-value
Age (years), mean ± SD	34.0 ± 6.5	36.1 ± 6.8	1.05 (0.98 - 1.13)	0.158
BMI (kg/m²), mean ± SD	28.2 ± 4.0	31.8 ± 4.5	1.22 (1.12 - 1.33)	< 0.001
Vertical Incision, n (%)	88 (47.8)	12 (75.0)	3.27 (1.08 - 9.87)	0.036
Wound Infection, n (%)	18 (9.8)	7 (43.8)	7.14 (2.45 - 20.80)	< 0.001
History of ≥ 2 Prior Cesareans, n (%)	38 (20.7)	7 (43.8)	3.00 (1.08 - 8.33)	0.035
Diabetes Mellitus, n (%)	8 (4.3)	2 (12.5)	3.13 (0.62 - 15.87)	0.169
Continuous Fascial Closure, n (%)	150 (81.5)	10 (62.5)	0.38 (0.14 - 1.03)	0.057

Table 3. *Statistical analysis of incisional hernia risk factors*

Variable	Adjusted OR	95% C I	p-value
BMI (per unit increase)	1.12	1.05 – 1.19	< 0.001
Vertical Incision	4.10	1.75 – 9.60	0.001
Postoperative Wound Infection	5.22	2.15 – 12.67	< 0.001
History of ≥ 2 Prior Cesareans	3.85	1.42 – 10.45	0.008
Continuous Fascial Closure	0.42	0.20 – 0.88	0.022

In the multivariable logistic regression model (Table 3), higher body mass index (per unit increase), vertical incision, postoperative wound infection, and a history of multiple (≥2) Cesarean sections remained significant independent risk factors. Continuous fascial closure was an independent protective factor.

Early Symptoms

Among the 16 patients diagnosed with an incisional hernia, the most commonly self-reported early symptoms before clinical confirmation were a palpable bulge or swelling (75%, 12/16), persistent ache or pain at the incision site (62.5%, 10/16), and discomfort during physical activity (50%, 8/16), as shown in Table 4.

Table 4. *Early symptoms reported before clinical diagnosis of incisional hernia (n = 16)*

Symptom	N	%
Palpable bulge or swelling	12	75.0
Persistent ache or pain at incision site	10	62.5
Discomfort during physical activity	8	50.0
Feeling of pressure or heaviness	6	37.5
Note: Patients could report more than one symptom.		

The observed difference in incidence between the Cesarean section (6.0%) and open gynecologic surgery (10.0%) groups is clinically significant and likely attributable to the substantially higher prevalence of midline incisions (70%) in the open gynecologic cohort compared to the CS group (15%), where the more robust Pfannenstiel incision predominated. These findings are consistent with the literature (10).

The strong association between higher Body Mass Index (BMI) and IH risk, with an adjusted odds ratio of 1.12 per unit, underscores the significant role of obesity in hernia development. Factors contributing to this risk include increased intra-abdominal pressure, reduced blood flow to the abdominal wall fascia from excess adipose tissue, and potentially poorer tissue quality and healing in obese patients (9). This finding emphasizes the importance of preoperative counseling and weight optimization, where feasible, as a key component of risk reduction strategies.

Our results strongly support the preferential use of transverse incisions, such as Pfannenstiel, over vertical midline incisions whenever surgically feasible. The adjusted odds ratio of 4.10 for a vertical incision highlights its biomechanical inferiority. Transverse incisions align with Langer's lines of skin tension, resulting in lower lateral tension on the fascial closure and promoting stronger healing (11). This is a modifiable surgical factor with substantial impact on long-term outcomes. Guitarte et al. (12) reported similar findings, identifying older age, hypertension, loop sutures, and cancer as risk factors for IH after vertical midline laparotomy.

Perhaps the most significant modifiable risk factor in our study was postoperative wound infection, which increased the odds of IH by over five-fold (OR 5.22). Surgical site infection (SSI) creates a local inflammatory environment that leads to collagenolysis, impaired fibroblast function, and ultimately fascial weakening (13,14). SSI rates for IH surgery range from 0.7% to 26.6% and are associated with local complications, prolonged treatment, and higher one-year recurrence, despite IH repair being classified as a clean surgical operation (15). These observations underscore the importance of strict adherence to SSI prevention bundles (14), including appropriate antibiotic prophylaxis, meticulous hemostasis, gentle tissue handling, maintenance of normothermia, and sterile technique (16). Vigilant postoperative wound care for early detection and management of infections is equally critical.

A novel and important finding of our study is the quantification of risk associated with multiple prior Cesarean sections. Patients with ≥ 2 previous CS had a nearly four-fold increased risk (OR 3.85). This emphasizes cumulative damage to the abdominal wall with each subsequent operation, as scar tissue retains only 70–80% of the tensile strength of native fascia (17, 18). These results highlight the need for meticulous surgical technique in repeat surgeries and inform patient discussions regarding cumulative risks of multiple abdominal procedures.

On a positive note, our study reinforces current best-practice guidelines for fascial closure (9,11). Continuous fascial closure with a slowly absorbable suture was protective (OR 0.42). This technique evenly distributes tension, creating a secure and biomechanically stable closure, unlike interrupted sutures that may create localized stress points and ischemia (16). This simple, evidence-based choice should be widely adopted to improve patient safety.

Beyond prevention, our findings on early symptomatology suggest clear opportunities for improving patient care. High frequencies of patient-reported early symptoms, specifically a palpable bulge (75%) and persistent pain (62.5%), indicate that patients often detect issues before clinical diagnosis. This supports implementing structured post-discharge education programs to teach high-risk patients how to perform careful self-examination and report "red flag" symptoms early (19). Such strategies could shorten the time to diagnosis and elective repair, reduce complications like obstruction or strangulation, and improve overall outcomes.

Limitations

The findings of this study may have limited generalizability to other populations or healthcare settings due to its single-center design. Physical activity level was based on self-report, which introduces the potential for recall and social desirability bias. While a 12-month follow-up is standard in IH research, it may miss hernias that manifest later; therefore, longer-term studies are needed to capture the true lifetime incidence. Finally, although our sample size was adequate for identifying major risk factors, it may be underpowered to detect the significance of rarer variables or more complex interactions.

CONCLUSION

This study successfully identified and categorized the main risk factors for incisional hernia after Cesarean and open gynecologic surgery. The predictors—obesity, vertical incisions, wound infections, and a history of multiple Cesareans—provide a clear profile for high-risk patients. These findings advocate for a multi-faceted approach encompassing:

1. Preoperative risk assessment and patient counseling,
2. The preferential use of transverse incisions and continuous fascial closure as standard technique,
3. Rigorous, protocol-driven SSI prevention, and
4. The implementation of post-discharge surveillance and patient education for high-risk individuals.

Future work should aim to validate these risk factors in larger, multi-center cohorts and to develop targeted interventions, such as prophylactic mesh augmentation or structured rehabilitation programs, to mitigate risk in these high-risk groups.

Abbreviations

IH – Incisional Hernia
CS – Cesarean Section
SSI – Surgical Site Infection
BMI – Body Mass Index
IQR – Interquartile Range
BTMC – Bin Tayyab Medical Complex

Acknowledgment: The authors thank the nursing staff and research coordinators at BTMC for their in-

valuable assistance with patient recruitment and data collection.

Financial Support: This research received no external funding or sponsorship.

Conflict of Interest Statement: The authors declare that there is no conflict of interest related to this paper.

Author Contribution & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. The project was conceptualized by Dr. Munir Menon and Dr. Zaheera Saadia. They were responsible for data collection, curation, and compilation of the original draft. Dr. Sajad Ahmad Salati reviewed and edited the Introduction, Discussion, and References sections. The project was supervised overall by Dr. Munir Menon.

Data Availability Statement: Requests to access the datasets should be directed to the corresponding author.

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

Sažetak

STRATIFIKACIJA FAKTORA RIZIKA I RANA DETEKCIJA INCIZIONALNIH HERNIJA NAKON CARSKOG REZA I OTVORENIH GINEKOLOŠKIH PROCEDURA: PROSPEKTIVNA OPSERVACIONA STUDIJA

Memon Munir Muhammad,[1, 2] Salati Ahmad Sajad,[3] Saadia Zaheera[4]

[1] Univerzitet Qassim, podružnica Buraidah, Medicinski fakultet, Katedra za hirurgiju, Kraljevina Saudijska Arabija
[2] Medicinski kompleks Bin Tayyab (BTMC), Hyderabad, Sindh, Pakistan
[3] Univerzitet Qassim, podružnica Unayzah, Medicinski fakultet, Katedra za hirurgiju, Kraljevina Saudijska Arabija
[4] Univerzitet Qassim, podružnica Buraidah, Medicinski fakultet, Katedra za ginekologiju, Kraljevina Saudijska Arabija

Uvod: Incizionalna hernija predstavlja značajnu komplikaciju abdominalnih operacija, koja dovodi do bola, funkcionalnih ograničenja i povećanih troškova zdravstvene zaštite. Cilj ove studije bio je identifikovati i rangirati faktore rizika za incizionalnu herniju kod pacijentkinja koje su imale carski rez ili otvorenu ginekološku operaciju, kao i proceniti strategije za njihovu ranu detekciju.

Metode: Od januara 2023. do juna 2025. sprovedena je prospektivna opservaciona studija u kojoj je učestvovalo 200 žena, svaka praćena tokom 12 meseci. Polovina pacijentkinja je imala carski rez (n = 100), dok je druga polovina imala otvorene ginekološke operacije (n = 100). Prikupljeni su podaci o demografskim karakteristikama, indeksu telesne mase, komorbiditetima, detaljima operacije i postoperativnim komplikacijama. Primarni ishod bio je incidenca incizionalne hernije tokom jedne godine, procenjena kliničkim pregledima nakon 6 nedelja, 6 meseci i 12 meseci.

Rezultati: Ukupna incidenca incizionalne hernije iznosila je 8,0% (16/200), sa 6,0% (6/100) nakon carskog reza i 10,0% (10/100) nakon otvorenih ginekoloških procedura. Multivarijabilna analiza identifikovala je sledeće nezavisne faktore rizika: viši indeks telesne mase (adjusted odds ratio 1,12 po jedinici, 95% CI 1,05–1,19, p < 0,001), vertikalni rez (odds ratio 4,10, 95% CI 1,75–9,60, p=0,001), postoperativnu infekciju rane (odds ratio 5,22, 95% CI 2,15–12,67, p<0,001) i dva ili više prethodnih carskih rezova (odds ratio 3,85, 95% CI 1,42–10,45, p = 0,008). Šivenje fascije produžnim šavom predstavljalo je zaštitni faktor (odds ratio 0,42, 95% CI 0,20–0,88, p = 0,022). Najčešći rani simptomi koje su pacijentkinje prijavile pre postavljanja dijagnoze bili su palpabilno ispupčenje (75%), postojan bol (62,5%) i nelagodnost tokom fizičkih aktivnosti (50%).

Zaključak: Viši indeks telesne mase, vertikalni rezovi, infekcija rane i više prethodnih carskih rezova predstavljaju značajne faktore rizika za incizionalnu herniju. Upotreba transverzalnih rezova i šivenje fascije produžnim šavom, kada je moguće, zajedno sa pažljivom postoperativnom negom rane i edukacijom pacijentkinja o samopregledu radi ranog prepoznavanja simptoma, može doprineti smanjenju rizika i omogućiti ranije otkrivanje kod pacijentkinja sa visokim rizikom.

***Ključne reči**:* Incizionalna hernija, carski rez, ginekološke operacije, faktori rizika, prospektivna studija, gojaznost, infekcija hirurškog mesta.

REFERENCES

1. Söderbäck H, Gunnarsson U, Hellman P, Sandblom G. Incisional hernia after surgery for colorectal cancer: a population-based register study. Int J Colorectal Dis. 2018; 33(10): 1411-7. doi: 10.1007/s00384-018-3124-5.

2. Fischer JP, Basta MN, Mirzabeigi MN, Bauder AR, Fox JP, Drebin JA, et al. A risk model and cost analysis of incisional hernia after elective, abdominal surgery based upon 12,373 cases: The case for targeted prophylactic intervention. Ann Surg. 2016; 263(5): 1010–7. doi: 10.1097/SLA.0000000000001394.

3. Shand AW, Chen JS, Schnitzler M, Roberts CL. Incisional hernia repair after caesarean section: a population-based study. Aust NZJ Obstet Gynaecol. 2015; 55(2): 170-5. doi: 10.1111/ajo.12270.

4. Paulsen CB, Zetner D, Rosenberg J. Incisional hernia after cesarean section: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2020; 244: 128-33. doi: 10.1016/j.ejogrb.2019.11.010.

5. Aabakke AJ, Krebs L, Ladelund S, Secher NJ. Incidence of incisional hernia after cesarean delivery: a register-based cohort study. PLoS One. 2014; 9(9): e108829. doi: 10.1371/journal.pone.0108829.

6. Bewö K, Österberg J, Löfgren M, Sandblom G. Incisional hernias following open gynecological surgery: a population-based study. Arch Gynecol Obstet. 2019; 299(5): 1313-9. doi: 10.1007/s00404-019-05069-0.

7. Franchi M, Ghezzi F, Buttarelli M, Tateo S, Balestreri D, Bolis P. Incisional hernia in gynecologic oncology patients: a 10-year study. Obstet Gynecol. 2001; 97(5 Pt 1): 696-700. doi: 10.1016/s0029-7844(01)01192-9.

8. Spear K, Davenport DL, Butler L, Plymale M, Roth JS. Comparison of incisional hernia rates between general and gynecological surgery procedures. Medicina (Kaunas). 2025; 61(3): 435. doi: 10.3390/medicina61030435.

9. Sanders DL, Pawlak MM, Simons MP, Aufenacker T, Balla A, Berger C, et al. Midline incisional hernia guidelines: the European Hernia Society. Br J Surg. 2023; 110(12): 1732-68. doi: 10.1093/bjs/znad284.

10. Kisielinski K, Conze J, Murken AH, Lenzen NN, Klinge U, Schumpelick V. The Pfannenstiel or so called "bikini cut": still effective more than 100 years after first description. Hernia. 2004; 8(3): 177–81. doi: 10.1007/s10029-004-0210-0.

11. Deerenberg EB, Henriksen NA, Antoniou GA, Antoniou SA, Bramer WM, Fischer JP, et al. Updated guideline for closure of abdominal wall incisions from the European and American Hernia Societies. Br J Surg. 2022; 109(12): 1239-50. doi: 10.1093/bjs/znac302.

12. Guitarte C, Grant J, Zhao H, Wang S, Ferriss JS, Hernandez E. Incisional hernia formation and associated risk factors on a gynecologic oncology service: an exploratory analysis. Arch Gynecol Obstet. 2016; 294(4): 805-11. doi: 10.1007/s00404-016-4100-3.

13. Thorup T, Tolstrup MB, Gögenur I. Reduced rate of incisional hernia after standardized fascial closure in emergency laparotomy. Hernia. 2019; 23(2): 341-6. doi: 10.1007/s10029-019-01893-0.

14. Berrevoet F. Prevention of incisional hernias after open abdomen treatment. Front Surg. 2018; 5: 11. doi: 10.3389/fsurg.2018.00011.

15. Juvany M, Hoyuela C, Trias M, Carvajal F, Ardid J, Martrat A. Impact of surgical site infections on elective incisional hernia surgery: a prospective study. Surg Infect. 2018; 19(3): 339-44. doi: 10.1089/sur.2017.233.

16. Dias Rasador AC, Mazzola Poli de Figueiredo S, Fernandez MG, Dias YJM, Martin RRH, da Silveira CAB, et al. Small bites versus large bites during fascial closure of midline laparotomies: a systematic review and meta-analysis. Langenbecks Arch Surg. 2024; 409(1): 104. doi: 10.1007/s00423-024-03293-0.

17. van Ramshorst GH, Nieuwenhuizen J, Hop WC, Arends P, Boom J, Jeekel J, et al. Abdominal wound dehiscence in adults: development and validation of a risk model. World J Surg. 2010; 34(1): 20-7. doi: 10.1007/s00268-009-0277-y.

18. Aylia FA, Khirie S, Steinberg D. Incisional hernia repair during cesarean section. Cureus. 2022; 14(4): e24121. doi: 10.7759/cureus.24121.

19. Sherer DM, Zinn H, Papavlassopulos A, Thompson M, Benton L, Filipovic A, et al. Early postpartum unilateral vulvar edema leading to diagnosis of a Pfannenstiel incisional hernia following cesarean delivery. Radiol Case Rep. 2024; 19(12): 6343-6. doi: 10.1016/j.radcr.2024.08.133.

Correspondence to/Autor za korespondenciju
Dr Muhammad Munir Memon,
Department of surgery, College of Medicine, Qassim University, Saudi Arabia.
email: m.ghafar@qu.edu.sa
Mob. Number 00966 542862377
Postal address
Building no. 8773, street.
Fahd ibn Sahl, Buraidah,
Qassim, KSA, 52379
ORCID Id
Muhammad Munir Memon 0000-0003-2501-3126
Salati Ahmad Sajad 0000-0003-2998-7542
Saadia Zaheera 0000-0001-5545-3902

How to cite this article: **Memon MM ,** Salati AS, Saadia Z. Risk factor stratification and early detection of incisional hernias after Cesarean and open gynecologic procedures: a prospective observational study. Sanamed. 2025; 20(3): 243-249. doi: 10.5937/sanamed0-61135.

SANAMED
2025; 20(3): 251–257
ISSN-1452-662X

DOI: 10.5937/sanamed0-61604
UDK: 616.718.19-001.5
ID: 183842825
Original article

AVULSION FRACTURES OF THE ANTERIOR ILIAC SPINE IN CHILDREN AND ADOLESCENTS: CLINICAL OUTCOMES OF NON-OPERATIVE TREATMENT

Božović Aleksandar,[1, 2] Jovanović Saša,[1, 2] Petrović Dušan,[1, 2] Denović Predrag,[2] Tabaković Dejan,[1, 3] Dulić Oliver,[4, 5] Milinkov Milan,[4, 5] Lalić Ivica[6]

[1] University of Priština in Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia
[2] Clinical Hospital Center Kosovska Mitrovica, Department of Orthopedic Surgery and Traumatology, Kosovska Mitrovica, Serbia
[3] Clinical Hospital Center Priština, Gračanica, Serbia
[4] University Clinical Center of Vojvodina, Clinic for Orthopedic Surgery and Traumatology, Novi Sad, Serbia
[5] University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia
[6] University Business Academy, Faculty of Pharmacy, Novi Sad, Serbia

Primljen/Received: 20. 09. 2025. Prihvaćen/Accepted: 11. 11. 2025. Online First: 24. 11. 2025.

Abstract: **Objective:** Avulsion fractures of the anterior iliac spine are injuries typically seen in physically active children and adolescents. There is no clear consensus regarding the optimal treatment, particularly concerning the degree of fragment displacement that warrants surgical intervention.

Aim: The aim of this study was to analyze the clinical outcomes of non-operative treatment of pelvic avulsion fractures in adolescents and to examine the relationship between patient age and rehabilitation duration.

Patients and Methods: A retrospective study was conducted on 12 adolescent patients with radiographically confirmed pelvic avulsion fractures. Data on age, fracture location, injury mechanism, treatment, and rehabilitation duration were collected and analyzed. All patients underwent non-operative management consisting of rest, analgesics, and crutch-assisted ambulation, followed by physical therapy.

Results: All patients were male, with a mean age of 12 years. The most common fracture site was the anterior inferior iliac spine (66.6%). All fractures healed without complications. Rehabilitation duration tended to be shorter in younger patients. Functional outcomes were excellent, with all patients returning to their pre-injury activity levels.

Conclusion: Non-operative treatment is an effective and safe approach for managing pelvic avulsion fractures in adolescents, even in cases with fragment displacement up to 15 mm. It provides excellent functional recovery without complications, supporting its use as the first-line treatment in this population.

Keywords: Avulsion fractures, Pelvis, Adolescents, Children, Treatment.

INTRODUCTION

Avulsion fractures of the pelvis are injuries that predominantly occur in active adolescents (1). In this age group, the strengthening of the lower limb musculature coincides with the development of secondary ossification centers (apophyses) (2). Pelvic fractures account for less than 1% of all pediatric fractures; however, up to 5% of children with blunt trauma sustain a pelvic fracture (3, 4). High-intensity concentric muscle contractions during activities such as running, kicking, and jumping generate substantial tensile forces transmitted through the muscle–tendon complex to the apophysis (5). As the weakest link in this chain, the apophysis is therefore prone to failure (6).

While most published studies emphasize pelvic fractures caused by high-energy mechanisms, the majority of pelvic fractures in children and adolescents actually result from low-energy trauma. These are typically stable pelvic ring injuries or avulsion injuries of the pelvic apophyses (Figure 1), usually presenting with sudden, sharp pain in the pelvic region, sometimes accompanied by an audible cracking sound (7). The pain often subsides with rest but intensifies with physical activity. On clinical examination, localized tenderness, swelling, and restricted range of motion are commonly observed (8).

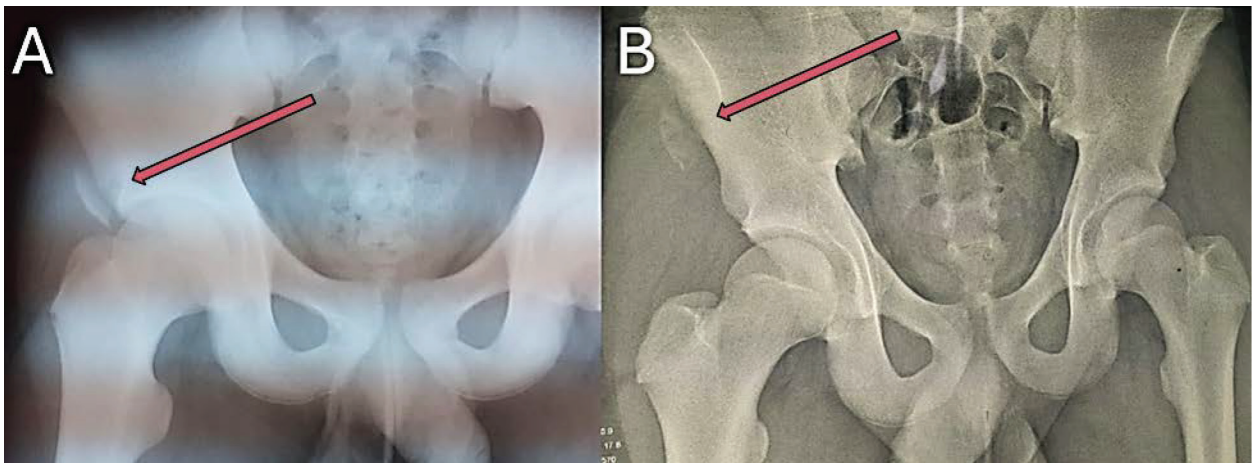


Figure 1. *A. Spina iliaca anterior inferior avulsion fracture. B. Spina iliaca anterior superior avulsion fracture (from the author's personal archive)*

The diagnosis of avulsion fractures relies on patient history—most report acute pain while jumping, kicking a ball, sprinting, or suddenly changing direction—combined with physical examination and radiographic evaluation. Differential diagnoses in pediatric patients include femoral head epiphysiolysis and musculotendinous injuries. Avulsion fractures may occur at several pelvic muscle attachment sites, including the rectus femoris insertion on the anterior inferior iliac spine (AIIS), the ischial tuberosity (IT), the sartorius insertion, the tensor fasciae latae attachment at the iliac crest (IC), and the iliopsoas insertion on the lesser trochanter (LT) (9).

Traditionally, treatment has been non-operative, consisting of analgesia, rest, and gradual rehabilitation. However, no clear consensus exists regarding surgical indications. The degree of fragment displacement and the patient's functional demands remain the primary factors guiding the decision for operative management (10).

Data on complications are limited, but reported issues include nonunion, neurological symptoms, infection, chronic pain, and heterotopic ossification. This lack of evidence highlights the need for further research to establish optimal treatment strategies, surgical criteria, and long-term outcomes in pediatric patients with pelvic avulsion fractures.

The aim of this study is to emphasize the importance of timely diagnosis, to analyze the distribution of pelvic avulsion fractures among adolescents according to age, and to examine the relationship between rehabilitation duration and age. Ultimately, our goal is to confirm that non-operative treatment is an effective approach for managing pelvic avulsion fractures, ensuring favorable outcomes without long-term complications.

MATERIALS AND METHODS

Following approval from the Ethics Committee of the Clinical Hospital Center Kosovska Mitrovica (No. 2389, 04/21/2023), a retrospective review was conducted on patients who presented to our department between January 2015 and January 2023 with symptoms of acute pelvic injury. A total of 12 adolescent patients with radiographically confirmed apophyseal avulsion fractures of the pelvis were included in the study.

Collected variables included age, sex, fracture location, laterality, mechanism of injury, degree of displacement, presence of prodromal symptoms, treatment approach, duration of orthopedic management, length of rehabilitation, and functional outcomes.

Descriptive statistics were used to summarize patient demographics and clinical outcomes. Continuous variables are reported as means and ranges, whereas categorical variables are presented as absolute numbers and percentages.

RESULTS

All 12 patients were male, aged 10–14 years (mean age: 12 years). The age distribution was as follows: two patients aged 10, two aged 11, six aged 12, and two aged 13. The mean age of the cohort was 11.7 ± 1.0 years (range: 10–13).

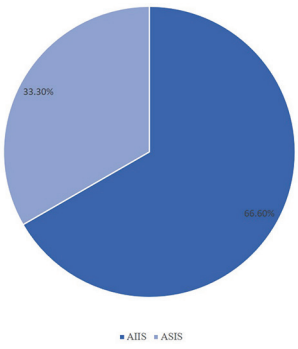


Figure 2. *Distribution of ASIS (anterior superior iliac spine) vs. AIIS (anterior inferior iliac spine) Avulsion Injuries*

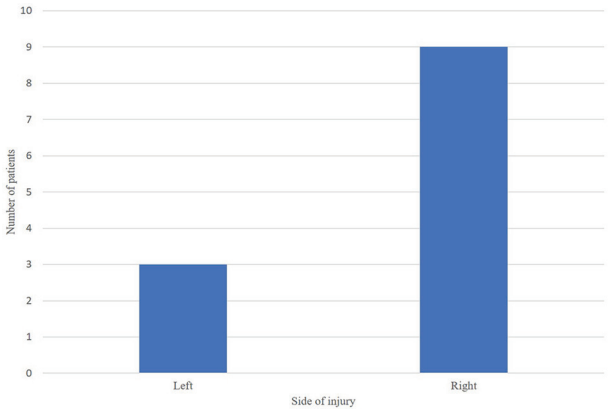


Figure 3. *Injury laterality*

Regarding fracture location, eight patients sustained anterior inferior iliac spine (AIIS) fractures, while four had anterior superior iliac spine (ASIS) fractures (Figure 2). Laterality analysis showed that 75% of injuries occurred on the right side and 25% on the left (Figure 3).

Most injuries (n = 10) occurred during football, while two were sustained during handball. None of the patients reported prodromal symptoms. One patient presented with a fracture displacement of 13 mm.

Clinically, all patients reported acute, sharp pain at the time of injury, limited hip range of motion, and difficulty walking independently. Radiographic imaging confirmed apophyseal displacement of up to 13 mm in all cases.

All patients were managed conservatively, including analgesics, bed rest with the hip flexed and slightly abducted, and ambulation with axillary crutches. Six patients (50%) underwent orthopedic treatment for five weeks, four (33%) for six weeks, and two (17%) for four weeks. The mean duration of orthopedic treatment was 5.2 ± 0.7 weeks (range: 4–6). Follow-up radiographs confirmed fracture healing in all cases, after which physical therapy was initiated (Figure 4).

Rehabilitation duration varied with age. Seven patients (58%) completed rehabilitation within four weeks, three (25%) within three weeks, and two (17%) within five weeks. The mean rehabilitation duration was 3.9 ± 0.7 weeks (range: 3–5). The majority of 12-year-olds completed rehabilitation within four weeks (Figure 5).

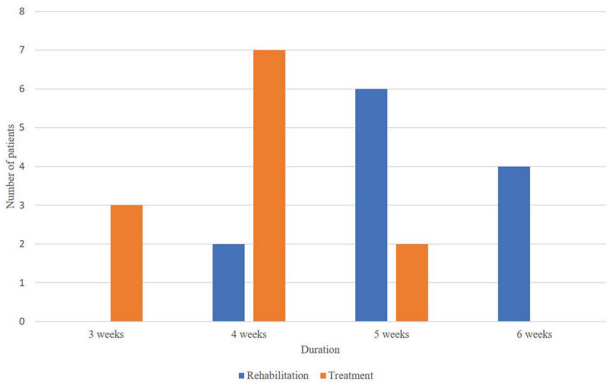


Figure 5. *Number of patients by duration (weeks) of treatment and rehabilitation*

All patients returned to their pre-injury activity levels within an average of nine weeks after the injury (range: 7–11). No complications were observed during treatment or follow-up.

DISCUSSION

Avulsion fractures of the pelvis in physically active adolescents represent a considerable challenge for orthopedic surgeons. At present, there is no clear consensus or evidence-based guideline regarding the optimal management of these injuries. Although our study does not specifically address the pathophysiology of avulsion fractures, it is important to highlight certain aspects.

The apophyses involved in these injuries appear to be particularly vulnerable prior to full ossification.

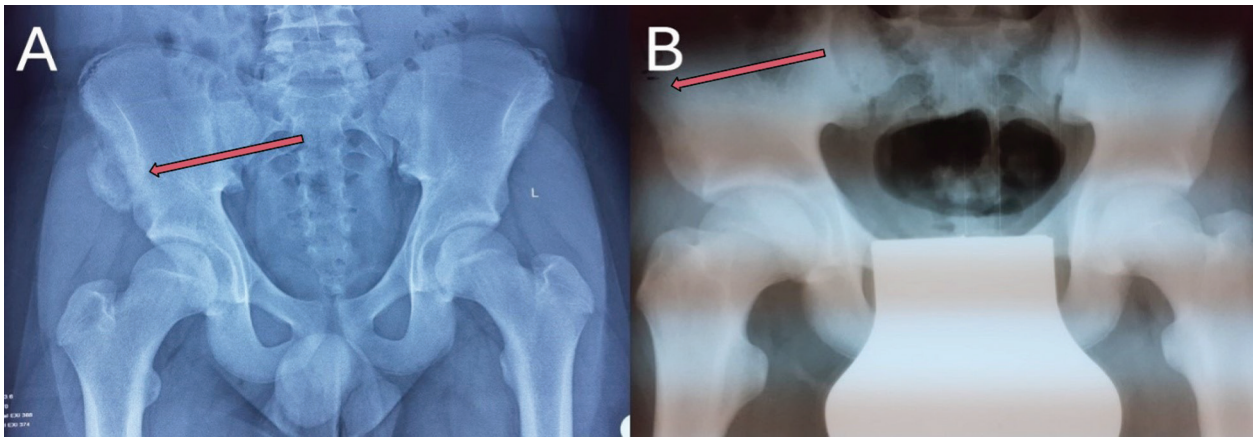


Figure 4. *A. Consolidated anterior superior iliac spine fracture following rehabilitation. B. Consolidated anterior inferior iliac spine fracture following rehabilitation (from the author's personal archive)*

During this phase, the apophyseal growth plate is exposed to an increased risk of improper ossification and subsequent avulsion, especially in adolescents undergoing periods of rapid growth. It is assumed that accelerated growth of the long bones in the lower extremities may lead to muscle contracture and tightness around the hip and knee, thereby amplifying the pathophysiological impact of eccentric muscle contractions on the apophysis (11). Furthermore, the increased frequency and intensity of physical activity in this population additionally contribute to apophyseal vulnerability (11).

The results of our study demonstrate that all participants were male. This gender distribution may be explained by the fact that, in Serbia, boys are generally more physically active than girls. The lower representation of girls in sports is influenced by cultural factors, lifestyle patterns, and lower overall participation in organized physical activities. Pelvic avulsion fractures remain a rare type of injury, most commonly occurring in physically active adolescents (12).

In adolescents, the epiphyseal plates are not yet fused, which makes them more susceptible to eccentric muscle contractions that alter the anatomical relationship between the growth plate and adjacent bone structures (13). In our cohort, the highest incidence of avulsion fractures was observed in 12-year-olds, representing 50% of all patients (n = 6). This may be explained by the fact that children at this age are often more physically active compared with their peers, while the epiphyseal growth plate still lacks closure zones.

To the best of our knowledge, no previous studies have examined the prevalence and laterality of pelvic avulsion fractures. In our series, slightly more injuries occurred on the right side (75%).

Our findings are consistent with other studies identifying running and kicking as the most frequent mechanisms of injury (8, 10-14). Schuett et al. reported that kicking is the most frequent cause of AIIS avulsion fractures, whereas running is the most common mechanism for ASIS avulsion fractures (15). All participants in our study presented with acute pain, limited active and passive range of motion, and inability to walk independently.

Diagnosis in our patients was based on the mechanism of injury obtained from history taking and confirmed with radiographic imaging, which demonstrated apophyseal displacement of up to 13 mm. Standard pelvic radiographs in two planes are recommended in cases of suspected pelvic avulsion fracture (14). In our series, no additional diagnostic modalities were required, as clinical examination consistently supported the diagnosis. However, other authors have emphasized that when plain radiographs are inconclusive, MRI or ultrasound may be useful to detect occult fractures or associated soft-tissue injuries (15). As a differential diagnosis, we initially considered epiphysiolysis of the femoral head, which was excluded by radiographic evaluation.

Other authors have suggested a broader spectrum of differential diagnoses (16, 17, 18). For example, Gidvani et al. reported eight cases of ischial tuberosity avulsion fractures that were initially misdiagnosed as muscle–tendon ruptures (19). Such misdiagnoses resulted in unnecessary and more extensive surgical procedures. These findings underline the importance of timely and accurate diagnosis to ensure appropriate management.

In pelvic avulsion fractures, displacement of bone fragments is often limited by the thick periosteum and surrounding pelvic fascia in adolescents. Consequently, non-operative management combined with a structured rehabilitation program is generally considered the preferred approach for treating non-displaced fractures (20).

In accordance with current treatment protocols, and given that the displacement of the apophysis in our cohort was 13 mm, we opted for non-operative treatment. Current evidence recommends conservative management for avulsion fractures with displacement up to 15 mm, with many studies confirming favorable functional outcomes. This strategy also avoids exposing adolescents to the risks associated with anesthesia. Our treatment protocol included analgesics, activity restriction, and two weeks of bed rest with proper limb positioning, followed by the use of crutches for 4–6 weeks (21).

In our study, six patients (50%) were treated for five weeks, four (33%) for six weeks, and two for four weeks. When analyzing the relationship between treatment duration and patient characteristics, we observed that the largest group—four patients aged 12 years—required five weeks of rehabilitation. This correlation may be explained by the higher activity levels and rapid growth characteristic of this age group, which increase their susceptibility to injury. Additionally, younger patients generally required shorter rehabilitation periods, with an average reduction of seven days compared with older adolescents. This observation supports the view that orthopedic treatment tends to be shorter in children than in older patients.

All patients used axillary crutches during the treatment period, which was crucial in partially neutralizing muscle forces during contraction, thereby reducing pain and preventing further displacement at the fracture site. The non-operative treatment we applied,

followed by structured physical therapy, resulted in excellent clinical and functional outcomes in all cases. Rehabilitation duration ranged between three and five weeks, depending on patient age and physical condition. Interestingly, the largest proportion of patients completing rehabilitation within four weeks were also 12 years old, consistent with the higher incidence of avulsion fractures at this age.

After two treatment sessions, patients were able to discontinue the use of crutches. Similar results were reported by Metzmaker et al., who successfully managed 27 cases of pelvic avulsion fractures using a structured five-phase rehabilitation protocol (22). Kjellin et al. treated adolescent athletes involved in sports that include sprinting, jumping, and sudden changes of direction (such as football, athletics, and gymnastics) using a conservative approach—rest, activity modification, analgesics, and gradual rehabilitation. Return to sports was permitted once pain subsided and muscle function normalized. Most patients recovered without lasting effects (23). In a review by Yanagisawa et al., a gradual approach to rehabilitation was emphasized, starting with pain management and progressing through mobility exercises, strengthening, and sport-specific training. Despite the prevalence of these injuries, the review highlighted a lack of new knowledge regarding pelvic sports injuries, with only fifteen articles published between 2013 and 2023 meeting the inclusion criteria (24).

Although conservative treatment is generally effective, it can occasionally have adverse effects on the patient's health in both the short and long term. However, in our cohort no complications were observed, and all patients successfully returned to their pre-injury activity levels. We attribute these outcomes to timely diagnosis, appropriate immobilization, and the implementation of structured physical therapy. These factors highlight the importance of taking such injuries seriously and ensuring that adolescents remain disciplined throughout the rehabilitation process to achieve optimal functional recovery.

When treating adolescents, it is also essential to consider their long-term well-being. Any compromise in the treatment protocol at this stage may result in complications that manifest later in life, particularly when patients assume physically demanding occupations. Reported potential complications include heterotopic ossification and femoroacetabular impingement (FAI) (25). Both conditions may lead to chronic pain in the fracture region and a consequent reduction in physical activity (26, 27).

In our study, functional results were excellent, and no complications occurred, further confirming that non-operative management is an appropriate treatment option for avulsion fractures with displacement up to 15 mm. These findings are consistent with previously published studies, which also support conservative treatment as the primary approach for minimally displaced pelvic avulsion fractures (28, 29).

CONCLUSION

Based on our research, we conclude that pelvic avulsion fractures most commonly occur in adolescents around the age of 12. Non-operative treatment, which in our cohort lasted an average of five weeks, followed by approximately four weeks of rehabilitation, resulted in excellent functional outcomes. Consistent with findings from the literature, our study supports the view that conservative management should be considered the first-line treatment for pelvic avulsion fractures with displacement up to 15 mm.

Financial Support: This research received no external funding or sponsorship.

Conflict of Interest Statement: The authors declare that there is no conflict of interest related to this paper.

Author Contribution & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. **Authors' contributions-AB:** study concept and design, data analysis, drafting of the manuscript; **SJ:** data collection, clinical management of patients, manuscript revision; **DP:** clinical follow-up of patients, review and correction of the manuscript; **PD:** diagnostics and radiological assessment of patients, collection of documentation; **DT:** study organization, statistical data processing; **OD:** analysis and interpretation of results, preparation of tables and figures; **MM:** corresponding author, final editing of the manuscript, coordination among authors; **IL:** professional and methodological support, language and technical editing of the manuscript.

Data Availability Statement: Requests to access the datasets should be directed to the corresponding author.

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

Sažetak

AVULZIONE FRAKTURE PREDNJE ILIJAČNE BODLJE KOD DECE I ADOLESCENATA: KLINIČKI ISHODI NEOPERATIVNOG LEČENJA

Božović Aleksandar,[1, 2] Jovanović Saša,[1, 2] Petrović Dušan,[1, 2] Denović Predrag,[2] Tabaković Dejan,[1, 3] Dulić Oliver,[4, 5] Milinkov Milan,[4, 5] Lalić Ivica[6]

[1] Univerzitet u Prištini sa privremenim sedištem u Kosovskoj Mitrovici, Medicinski fakultet, Kosovska Mitrovica, Srbija
[2] Kliničko bolnički centar Kosovska Mitrovica, Klinika za ortopediju i traumatologiju, Kosovska Mitrovica, Srbija
[3] Kliničko bolnički centar Priština, Gračanica, Srbija
[4] Univerzitetski klinički centar Vojvodine, Klinika za ortopedsku hirurgiju i traumatologiju, Novi Sad, Srbija
[5] Univerzitet u Novom Sadu, Medicinski fakultet, Novi Sad, Srbija
[6] Univerzitet Privredna akademija u Novom Sadu, Farmaceutski fakultet, Novi Sad, Srbija

Uvod: Avulzione frakture prednje ilijačne spine predstavljaju povrede tipične za fizički aktivnu decu i adolescente. Još uvek ne postoji jasan konsenzus o optimalnom načinu lečenja, posebno kada je reč o stepenu dislokacije fragmenta koji zahteva hiruršku intervenciju.

Cilj: Cilj rada je bio da se analiziraju klinički ishodi neoperativnog lečenja avulzionih fraktura karlice kod adolescenata i da se ispita odnos između uzrasta i trajanja rehabilitacije.

Materijal i metode: Sprovedena je retrospektivna studijana 12 adolescentnih pacijenata sa radiografski potvrđenim avulzionim frakturama karlice. Analizirani su podaci o uzrastu, lokalizaciji preloma, mehanizmu povrede, načinu lečenja i trajanju rehabilitacije. Svi pacijenti su lečeni neoperativno – mirovanje, analgetici i upotreba štaka, a potom fizikalna terapija.

Rezultati: Svi pacijenti su bili muškog pola, prosečne starosti 12 godina. Najčešće mesto preloma bila je prednja donja ilijačna spina (66,6%). Svi prelomi su zarasli bez komplikacija. Kod mlađih pacijenata rehabilitacija je trajala kraće. Funkcionalni ishodi bili su odlični, sa povratkom svih pacijenata na nivo aktivnosti pre povrede.

Zaključak: Neoperativno lečenje je efikasan i bezbedan pristup u terapiji avulzionih fraktura karlice kod adolescenata, čak i kod dislokacija fragmenta do 15 mm. Ovaj pristup omogućava odličan funkcionalni oporavak bez komplikacija i treba ga smatrati metodom prvog izbora u ovoj populaciji.

Ključne reči: avulzione frakture, karlica, adolescent, dete, lečenje.

REFERENCES

1. Schiller J, DeFroda S, Blood T. Lower extremity avulsion fractures in the pediatric and adolescent athlete. J Am AcadOrthop Surg. 2017; 25(4): 251-9. doi:10.5435/jaaos-d-15-00328.

2. Ghanem IB, Rizkallah M. Pediatric avulsion fractures of pelvis: current concepts. Curr Opin Pediatr. 2018; 30(1): 78-83. doi: 10.1097/mop.0000000000000575.

3. Orthobullets. Pediatric pelvis fractures [Internet]. Orthobullets; 2025 [cited 2025 Oct 26]. Available from: https://www.orthobullets.com/pediatrics/3000/pelvis-fractures--pediatric.

4. DeFrancesco CJ, Sankar WN. Traumatic pelvic fractures in children and adolescents. Semin Pediatr Surg. 2017; 26(1): 27-35. doi:10.1053/j.sempedsurg.2017.01.006.

5. Vlahek P, Matijević V. Lower extremity injuries in novice runners: incidence, types, time patterns, sociodemographic and motivational risk factors in a prospective cohort study. Acta Clin Croat. 2018; 57(1): 31–8. doi:10.20471/acc.2018.57.01.04.

6. Calderazzi F, Nosenzo A, Galavotti C, Menozzi M, Pogliacomi F, Ceccarelli F. Apophyseal avulsion fractures of the pelvis: a review. Acta Biomed. 2018; 89(4): 470–6. doi: 10.23750/abm.v89i4.7632.

7. Anduaga I, Seijas R, Perez-Bellmunt A, Casasayas O, Alvarez P. Anterior iliac spine avulsion fracture treatment options in young athletes. J Invest Surg. 2020; 33(2): 159–63. doi: 10.1080/08941939.2018.1483447.

8. Eberbach H, Hohloch L, Feucht MJ, Konstantinidis L, Sudkamp NP, Zwingmann J. Operative versus conservative treatment of apophyseal avulsion fractures of the pelvis in adolescents: a systematic review with meta-analysis of clinical outcome and return to sports. BMC Musculoskelet Disord. 2017; 18(1): 162. doi:10.1186/s12891-017-1527-z.

9. Willinger L, Schanda JE, Lorenz S, Imhoff AB, Buchmann S. Surgical treatment of two adolescent athletes with dislocated avulsion fracture of the anterior superior iliac spine (ASIS). Arch Orthop Trauma Surg. 2017; 137(2): 173–7. doi: 10.1007/s00402-016-2596-4.

10. Best R, Meister A, Huth J, Becker U, Meier M. Surgical repair techniques, functional outcome, and return to sports after apophyseal avulsion fractures of the ischial tuberosity in adolescents. Int Orthop. 2021; 45(8): 1853–61. doi: 10.1007/s00264-021-04959-w.

11. Longo UG, Ciuffreda M, Locher J, Maffulli N, Denaro V. Apophyseal injuries in children's and youth sports. Br Med Bull. 2016; 120(1): 139-57. doi: 10.1093/bmb/ldw041.

12. Sinikumpu JJ, Hetsroni I, Schilders E, Lempainen L, Serlo W, Orava S. Operative treatment of pelvic apophyseal avulsions in adolescent and young adult athletes: a follow-up study. Eur J Orthop Surg Traumatol. 2018; 28(3): 423–9. doi: 10.1007/s00590-017-2074-x.

13. Caine D, DiFiori J, Maffulli N. Physeal injuries in children's and youth sports: reasons for concern? Br J Sports Med. 2006; 40(9): 749-60. doi: 10.1136/bjsm.2005.017822.

14. Cirimele V, D'Amone G, Stellato L, Ferrini A, Gregori P, Faiella E. Magnetic resonance imaging in the evaluation of avulsion injuries of the pelvis and hip in adolescent professional footballers: a case series. J Orthop Case Rep. 2024; 14(5): 147-52. doi: 10.13107/jocr.2024.v14.i05.4466.

15. Schuett DJ, Bomar JD, Pennock AT. Pelvic apophyseal avulsion fractures: a retrospective review of 228 cases. J Pediatr Orthop. 2015; 35(6): 617–23. doi: 10.1097/bpo.0000000000000328.

16. Malina RM, Peña Reyes ME, Eisenmann JC, Horta L, Rodrigues J, Miller R. Height, mass and skeletal maturity of elite Portuguese soccer players aged 11-16 years. J Sports Sci. 2000; 18(9): 685–93. doi: 10.1080/02640410050120069.

17. Ferraro SL, Batty M, Heyworth BE, Cook DL, Miller PE, Novais EN. Acute pelvic and hip apophyseal avulsion fractures in adolescents: a summary of 719 cases. J Pediatr Orthop. 2023; 43(4): 204–10. doi: 10.1097/bpo.0000000000002355.

18. Ruffing T, Rückauer T, Bludau F, Hofmann A, Muhm M, Suda AJ. Avulsion fracture of the lesser trochanter in adolescents. Injury. 2018; 49(7): 1278–81. doi: 10.1016/j.injury.2018.04.030.

19. Gidwani S, Jagiello J, Bircher M. Avulsion fracture of the ischial tuberosity in adolescents - an easily missed diagnosis. BMJ. 2004; 329(7457): 99-100. doi: 10.1136/bmj.329.7457.99.

20. Otto A, Banke IJ, Mehl J, Beitzel K, Imhoff AB, Scheiderer B. Retrograde fixation of the lesser trochanter in the adolescent: new surgical technique and clinical results of two cases. Arch Orthop Trauma Surg. 2019; 139(4): 537–45. doi: 10.1007/s00402-018-3091-x.

21. Cai W, Xie Y, Su Y. Comparison of non-surgical and surgical treatment using absorbable screws in anterior-superior iliac spine avulsion fractures with over 1.5 cm displacement. OrthopTraumatol Surg Res. 2020; 106(8): 1299–304. doi: 10.1016/j.otsr.2020.02.014.

22. Metzmaker JN, Pappas AM. Avulsion fractures of the pelvis. Am J Sports Med. 1985; 13(5): 349–58. doi: 10.1177/036354658501300510.

23. Kjellin I, Stadnick ME, Awh MH. Orthopaedic magnetic resonance imaging challenge: apophyseal avulsions at the pelvis. Sports Health. 2010; 2(3): 247-51. doi: 10.1177/1941738109347976.

24. Yanagisawa Y, Yamazaki M. Rehabilitation for returning to sports in individuals with sports-induced pelvic injuries—a narrative review. J Phys Fitness Sports Med. 2024; 13(4): 125-9. doi: 10.7600/jpfsm.13.125.

25. Čengić T, Jurković D, Hajsok H, Smoljanović T, Novosel L, Rotim K, et al. Hip arthroscopy: residual cam deformity combined with loose bony fragment in hip capsule. Acta Clin Croat. 2021; 60(4): 777-82. doi:10.20471/acc.2021.60.04.28.

26. Di Maria F, Testa G, Sammartino F, Sorrentino M, Petrantoni V, Pavone V. Treatment of avulsion fractures of the pelvis in adolescent athletes: a scoping literature review. Front Pediatr. 2022; 10: 947463. doi: 10.3389/fped.2022.947463.

27. Novais EN, Riederer MF, Provance AJ. Anterior inferior iliac spine deformity as a cause for extra-articular hip impingement in young athletes after an avulsion fracture: a case report. Sports Health. 2018; 10(3): 272–6. doi: 10.1177/1941738117744547.

28. Ferlic PW, Sadoghi P, Singer G, Kraus T, Eberl R. Treatment for ischial tuberosity avulsion fractures in adolescent athletes. Knee Surg Sports Traumatol Arthrosc. 2013; 22(4): 893–7. doi:10.1007/s00167-013-2570-4.

29. Su Y, Chen K, Qin J. Retrospective study of open reduction and internal fixation of lateral humeral condyle fractures with absorbable screws and absorbable sutures in children. Medicine (Baltimore). 2019; 98(44): e17850. doi: 10.1097/md.0000000000017850.

Correspondence to/Autor za korespondenciju
Milan Milinkov
Bulevar Kralja Petra I 47 Street
21000 Novi Sad, Serbia
E-mail: milan.milinkov@mf.uns.ac.rs

ORCID IDs
Aleksandar Božović - 0000-0001-9338-9171
Dušan Petrović - 0000-0002-8614-0527
Dejan Tabaković - 0009-0001-0001-132X
Oliver Dulić - 0000-0002-5914-9956
Milan Milinkov - 0000-0001-9662-7403
Ivica Lalić - 0000-0001-6292-6608
Saša Jovanović - 0000-0001-7107-5104
Predrag Denović - 0009-0009-8660-1010

How to cite this article: Božović A, Jovanović S, Petrović D, Denović P, Tabaković D, Dulić O, Milinkov M, Lalić I. Avulsion fractures of the anterior iliac spine in children and adolescents: clinical outcomes of non-operative treatment. Sanamed. 2025; 20(3): 251-257. doi: 10.5937/sanamed0-61604.

SANAMED
2025; 20(3): 259–267
ISSN-1452-662X

DOI: 10.5937/sanamed0-61650
UDK: 616.132-007.271-074
ID: 183851273
Original article

EVALUATION OF HEMODYNAMIC AND BIOMARKER CHANGES IN PATIENTS UNDERGOING SURGICAL AORTIC VALVE REPLACEMENT

Slaveski Dimce,[1] Lončar-Stojiljković Dragana,[1, 2] Gavrilovska Brzanov Aleksandra,[3, 4] Bozhinovska Marija,[5] Sulejmani Haris,[4] Jovanovski Srceva Marija[3, 4]

[1] University of Banja Luka, Faculty of Medicine, Banja Luka, Bosnia and Herzegovina
[2] Institute for Cardiovascular Diseases Dedinje, Belgrade, Serbia
[3] University Clinic for Traumatology, Orthopedic Diseases, Anesthesiology, Reanimation and Intensive Care, and Emergency Medicine, Skopje, North Macedonia
[4] Ss. Cyril and Methodius University in Skopje, Faculty of Medicine, Skopje, North Macedonia
[5] University Medical Centre Ljubljana, Clinical Department of Anaesthesiology and Perioperative Intensive Therapy, Ljubljana, Slovenia

Primljen/Received: 23. 09. 2025. Prihvaćen/Accepted: 11. 11. 2025. Online First: 24. 11. 2025.

Abstract: **Background:** Aortic stenosis (AS) is a systemic disease characterized by valvular obstruction, ventricular remodeling, and perioperative vulnerability to oxygen supply–demand imbalance. This study evaluated perioperative metabolic and biomarker dynamics and early postoperative outcomes in patients undergoing surgical aortic valve replacement (AVR).

Patients and Methods: A prospective observational study was conducted on 60 consecutive adults with severe AS who underwent surgical AVR at a single center. Demographics, anthropometric data, intraoperative variables, complications, and pre- and postoperative hemodynamic and laboratory parameters were evaluated. Postoperatively, the following were assessed at 6 and 24 hours: mean arterial pressure (MAP), arterial oxygen saturation (SaO_2), partial pressure of oxygen (PaO_2), pH, partial pressure of carbon dioxide ($PaCO_2$), hemoglobin (Hb), lactate, and creatine kinase–MB isoenzyme (CK-MB). Continuous data are presented as mean ± standard deviation (SD) or median (interquartile range, IQR). Paired t-tests were used to compare values between 6 and 24 hours.

Results: The mean age was 69.9 ± 7.3 years; 58.3% were male. Mean anesthesia and operation times were 151.5 ± 21.8 and 126.8 ± 20.6 minutes, respectively; mean cardiopulmonary bypass (CPB) and cross-clamp times were 78.3 ± 17.6 and 58.5 ± 16.7 minutes. Nearly half of the patients (46.7%) had no postoperative complications; others experienced bleeding (16.7%), arrhythmias requiring therapy (6.7%), permanent pacemaker implantation (8.3%), re-exploration (6.7%), infection (8.3%), respiratory failure (3.3%), or renal failure (3.3%). From 6 to 24 hours postoperatively, lactate decreased (2.34 ± 0.96 → 1.87 ± 0.98 mmol/L; $p = 0.006$) and CK-MB declined (52.5 ± 34.2 → 39.0 ± 30.8 U/L; $p = 0.001$), while Hb increased (103.5 ± 10.1 → 120.1 ± 22.9 g/L; $p < 0.001$). pH decreased modestly (7.396 ± 0.057 → 7.365 ± 0.065; $p = 0.015$). MAP, SaO_2, PaO_2, and $PaCO_2$ showed no significant changes. The median hospital stay was 7 days (IQR 6–8).

Conclusions: In patients undergoing surgical AVR for AS, early postoperative trends demonstrated an improving metabolic profile (lower lactate) and biomarker normalization (CK-MB) with stable oxygenation, alongside low-to-moderate complication rates and a consistent 7-day median stay. Integrating perioperative oxygen-balance markers and cardiac biomarkers with imaging and left ventricular hypertrophy (LVH) assessment may refine timing and risk stratification for intervention. Prospective studies with standardized imaging and longer follow-up are warranted to link early metabolic recovery with ventricular remodeling and clinical outcomes.

Keywords: aortic stenosis, aortic valve replacement, lactate, creatine kinase–MB isoenzyme, biomarkers.

INTRODUCTION

Aortic stenosis (AS) is one of the most common and clinically significant valvular diseases, with incidence rising in parallel with aging populations and comorbid cardiovascular conditions (1, 2). The 2021

ESC/EACTS Guidelines emphasize timely diagnosis, accurate risk stratification, and balancing surgical and transcatheter aortic valve replacement (TAVR) options (1). The disease is increasingly recognized as a systemic process involving valve calcification, ventricular remodeling, and vascular alterations—often referred to as the "triumvirate" of valve, ventricle, and vessel (3).

Left ventricular hypertrophy (LVH), a hallmark of chronic pressure overload in AS, carries prognostic implications beyond valvular obstruction (4, 5). While surgical or transcatheter intervention can promote regression, recovery is variable, and higher preoperative left ventricular mass index (LVMI) has been associated with residual hypertrophy and adverse outcomes (6).

Advances in multi-modality imaging provide detailed evaluation of AS severity and myocardial adaptation. Echocardiography remains the cornerstone for grading, while computed tomography (CT) calcium scoring is indispensable for TAVR planning (7). Cardiovascular magnetic resonance (CMR) adds prognostic value by detecting diffuse fibrosis and extracellular matrix remodeling (8).

Biomarkers complement imaging in perioperative management. Lactate and creatine kinase–MB (CK-MB) reflect metabolic and myocardial recovery after intervention, while troponin and multimarker strategies predict adverse outcomes (9, 10). Perioperative studies further highlight the importance of maintaining oxygen supply–demand balance and myocardial protection during anesthesia and cardiopulmonary bypass (11, 12).

Finally, landmark trials and meta-analyses have refined the timing of intervention, particularly in asymptomatic severe AS. Evidence suggests that earlier AVR in selected patients improves outcomes (13, 14). In this context, surgical AVR continues to provide reliable results with acceptable complication rates, while TAVR expands treatment options for both high- and low-risk patients (15, 16).

PATIENTS AND METHODS

This was a prospective descriptive study that included 60 consecutive patients with severe aortic stenosis (AS) who underwent surgical aortic valve replacement (AVR) at the Clinic for Cardiac Surgery, Acibadem-Sistina Hospital, Skopje, North Macedonia, between October 2024 and April 2025. Patients were eligible if they were 18 years of age or older, had echocardiographically confirmed severe AS, and had complete perioperative documentation. Those undergoing concomitant major cardiac procedures or those with incomplete data were excluded.

Data were obtained from institutional medical records, anesthesia charts, surgical protocols, and laboratory reports. The data collector was blinded to perioperative management and the clinical course of the patients. Demographic information included age and sex, while baseline clinical and anthropometric characteristics comprised weight, height, body mass index (BMI), and American Society of Anesthesiologists (ASA) classification. Intraoperative variables included anesthesia and operation duration, cardiopulmonary bypass (CPB) and cross-clamp times, lowest hemoglobin (Hb), hematocrit (Hct), and body temperature during CPB, norepinephrine requirements, cardioplegia regimen, transfusion requirements, cardiac rhythm changes, and number of defibrillations required.

All patients underwent full sternotomy with cardiopulmonary bypass, with the flow rate set to 2.2–2.4 L/min/BSA, using cold blood cardioplegia administered at 15- to 20-minute intervals to achieve cardiac arrest and protect the myocardium during surgery. Postoperative complications were also recorded, including bleeding, re-exploration, arrhythmias, permanent pacemaker implantation, infections, respiratory failure, and renal failure.

Preoperative echocardiographic and laboratory measurements included aortic valve area (AVA), interventricular septal and posterior wall thickness, peak velocity (Vmax), Hb, Hct, arterial oxygen saturation (SaO_2), arterial partial pressure of oxygen (PaO_2), pH, arterial partial pressure of carbon dioxide ($PaCO_2$), lactate, and creatine kinase–MB isoenzyme (CK-MB). Postoperative hemodynamic and laboratory data were recorded at 6 and 24 hours after surgery, including mean arterial pressure (MAP), SaO_2, PaO_2, pH, $PaCO_2$, Hb, lactate, and CK-MB. The length of hospital stay (LOS) was also analyzed.

A detailed description of the surgical technique will be added once provided by the surgical team and will include the approach to cannulation, prosthetic valve implantation, cardioplegia administration, and weaning from CPB.

Continuous variables were summarized as mean ± standard deviation (SD), median with interquartile range (IQR), and minimum–maximum values. The normality of distribution was assessed using the Shapiro–Wilk test. Comparisons between sexes were performed using the Mann–Whitney U test, while changes between postoperative values at 6 and 24 hours were analyzed using the paired t-test. Categorical variables were expressed as frequencies and percentages. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 60 patients with severe aortic stenosis undergoing surgical aortic valve replacement during the study period were included. The results are presented in six structured tables, covering demographic

Table 1. *Demographics by sex*

Variable	Male (N = 35)	Female (N = 25)	Total (N = 60)
Age, years (Mean ± SD)	68.34 ± 7.51	71.96 ± 6.65	69.85 ± 7.33
Median (IQR)	69 (64–74)	73 (68–77)	70 (66–75)
Min–Max	49–80	54–80	49–80

data, baseline anthropometric and clinical characteristics, operative and intraoperative parameters, postoperative complications, preoperative echocardiographic and laboratory values, and postoperative hemodynamic and laboratory outcomes.

The cohort consisted of 35 men (58.3%) and 25 women (41.7%), with a mean age of 70 years (range: 49–80). No significant sex differences were observed in age distribution (Table 1).

Baseline anthropometric and clinical characteristics showed an overweight cohort (mean BMI: 28 kg/m^2), with all patients classified as ASA III (Table 2).

Operative parameters demonstrated mean anesthesia and operation times of approximately 150 and 127 minutes, respectively. Cardiopulmonary bypass (CPB) and cross-clamp durations averaged 78 and 59 minutes. The lowest hemoglobin and hematocrit values on bypass were 9 g/dL and 27%, respectively (Table 3).

Table 2. *Baseline anthropometric and clinical characteristics of 60 patients*

Variable	Total (N = 60)
BMI, kg/m^2 (Mean ± SD)	28.16 ± 3.96
Median (IQR)	28.2 (24.9–31.2)
Weight, kg (Mean ± SD)	80.27 ± 13.15
Median (IQR)	81 (70.3–89.8)
Height, cm (Mean ± SD)	168.67 ± 8.02
Median (IQR)	168 (164–175.8)

BMI – Body Mass Index;SD – Standard Deviation;IQR – Interquartile Range.

Table 3. *Operative and intraoperative continuous parameters*

Variable	Mean ± SD	Range
Anesthesia time, min	151.5 ± 21.8	110–195
Operation time, min	126.8 ± 20.6	88–179
CPB time, min	78.3 ± 17.6	46–127
Cross-clamp time, min	58.5 ± 16.7	24–100
Lowest Hb on CPB, g/dL	8.95 ± 1.22	6.3–12.5
Lowest Hct on CPB, %	27.2 ± 3.6	19–37
Lowest temperature, °C	35.1 ± 0.4	34.3–36.2
Norepinephrine dose, µg/kg/min	125.0 ± 203.0	0–987.5

CPB – Cardiopulmonary Bypass; Hb – Hemoglobin;Hct – Hematocrit; °C – Degrees Celsius; µg/kg/min – Micrograms per kilogram per minute; SD – Standard Deviation.

Categorical intraoperative findings, including cardioplegia regimens, transfusion requirements, rhythm changes, and defibrillation needs, are summarized in Table 4.

Nearly half of the patients (46.7%) had an uncomplicated postoperative course. The most common complications were bleeding (16.7%), arrhythmias (6.7%), and infections (8.3%), while respiratory and renal failure were rare (3.3% each). Details are shown in Table 5. The distribution of age, BMI, body weight, height, anesthesia and operation duration, CPB, and cross-clamp times is illustrated in Figure 1.

Table 4. *Operative and intraoperative categorical parameters*

Variable	Category	n (%)
Cardioplegia doses	2	6 (10.0)
	3	24 (40.0)
	4	24 (40.0)
	5	6 (10.0)
RBC transfusion	0	41 (68.3)
	1	17 (28.3)
	2	2 (3.3)
FFP transfusion	0	44 (73.3)
	1	16 (26.7)
Cryoprecipitate	0	50 (83.3)
	1	10 (16.7)
Platelet transfusion	0	56 (93.3)
	1	4 (6.7)
Rhythm	Sinus rhythm (SR)	40 (66.7)
	Pacemaker (PM)	12 (20.0)
	Atrial fibrillation (AF)	8 (13.3)
Defibrillation	0	22 (36.7)
	1	23 (38.3)
	2	8 (13.3)
	≥ 3	7 (11.7)

Table 5. *Postoperative complications*

Complication	n (%)
None	28 (46.7)
Bleeding	10 (16.7)
Re-exploration	4 (6.7)
Permanent pacemaker	5 (8.3)
Arrhythmia (Amiodarone/Cardioversion)	4 (6.7)
Respiratory failure	2 (3.3)
Infection	5 (8.3)
Renal failure	2 (3.3)

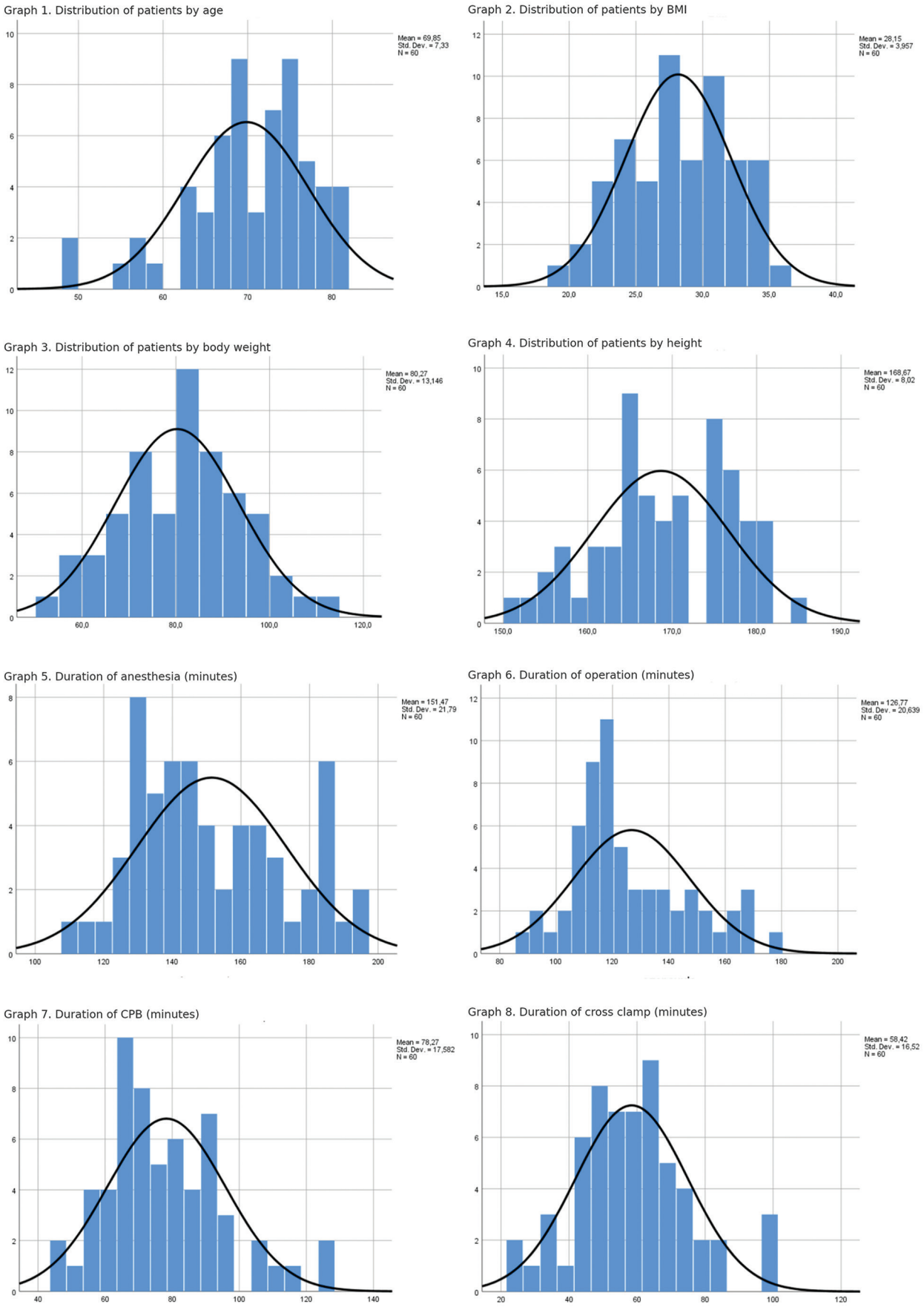


Figure 1. *Histogram distribution of demographic and intraoperative variables*

Table 6. *Preoperative echocardiographic and laboratory parameters*

Variable	Mean ± SD	Median (IQR)	Min–Max
AVA, cm^2	0.713 ± 0.142	0.75 (0.60–0.80)	0.5–0.9
IVSd, mm	11.35 ± 4.00	10.0 (7.25–15.0)	6–18
Posterior wall, mm	10.90 ± 3.25	10.0 (8.0–14.0)	6–22
Vmax, m/s	4.717 ± 0.246	4.75 (4.60–4.90)	4.2–5.2
Hemoglobin, g/L	128.97 ± 18.63	131.0 (115.0–140.8)	81–170
Hematocrit, %	38.01 ± 4.93	38.3 (34.6–42.1)	27.4–48
SaO_2, %	95.23 ± 2.12	95.0 (95.0–96.0)	87–99
PaO_2, mmHg	79.27 ± 8.75	80.6 (72.9–85.6)	59.1–96.5
pH	7.388 ± 0.048	7.395 (7.350–7.428)	7.27–7.48
$PaCO_2$, mmHg	38.39 ± 3.95	38.8 (35.1–41.2)	30.4–47.4
Lactate, mmol/L	1.077 ± 0.441	1.0 (0.7–1.4)	0.4–2.3
CK-MB, U/L	52.62 ± 19.41	53.0 (36.3–64.0)	18–97

AVA – Aortic Valve Area; IVSd – Interventricular Septal Thickness in Diastole; Vmax – Peak Aortic Jet Velocity; Hb – Hemoglobin; Hct – Hematocrit; SaO_2 – Arterial Oxygen Saturation; PaO_2 – Partial Pressure of Oxygen in Arterial Blood; pH – Hydrogen Ion Concentration (acid–base balance); $PaCO_2$ – Partial Pressure of Carbon Dioxide in Arterial Blood; CK-MB – Creatine Kinase–Myocardial Band Isoenzyme; SD – Standard Deviation; IQR – Interquartile Range.

Table 7. *Postoperative hemodynamic, laboratory, and outcome parameters*

Variable	6h Post-op (Mean ± SD / Median [IQR])	24h Post-op (Mean ± SD / Median [IQR])	Min–Max	p value
MAP, mmHg	79.3 ± 10.2 / 77.5 (72.3–87.0)	81.8 ± 9.9 / 80.0 (75–88)	63–110 / 65–105	0.120 (ns)
Lactate, mmol/L	2.34 ± 0.96 / 2.15 (1.7–3.0)	1.87 ± 0.98 / 1.7 (1.0–2.5)	0.7–5.2 / 0.5–4.5	0.006
CK-MB, U/L	52.5 ± 34.2 / 50.5 (39–73)	39.0 ± 30.8 / 39.0 (27–56.8)	26–163 / 20–158	0.001
Hb, g/L	103.5 ± 10.1 / 101.5 (95–112.8)	120.1 ± 22.9 / 114.5 (101.3–141.8)	87–127 / 87–168	< 0.001
SaO_2, %	99.2 ± 0.98 / 99.0 (99–100)	99.4 ± 1.20 / 100 (100–100)	96–100 / 95–100	0.294 (ns)
PaO_2, mmHg	141.5 ± 25.4 / 143.0 (122.3–162.8)	136.0 ± 29.4 / 138.0 (110.5–155.8)	94–193 / 85–195	0.258 (ns)
pH	7.396 ± 0.057 / 7.405 (7.38–7.43)	7.365 ± 0.065 / 7.380 (7.33–7.41)	7.22–7.51 / 7.21–7.45	0.015
$PaCO_2$, mmHg	41.9 ± 2.77 / 41.8 (39.8–43.4)	42.8 ± 4.45 / 42.7 (40.6–45.3)	36.4–50.0 / 30.2–54.0	0.133 (ns)

MAP – Mean Arterial Pressure; Hb – Hemoglobin; SaO_2 – Arterial Oxygen Saturation; PaO_2 – Partial Pressure of Oxygen in Arterial Blood; pH – Hydrogen Ion Concentration; $PaCO_2$ – Partial Pressure of Carbon Dioxide in Arterial Blood; CK-MB – Creatine Kinase–Myocardial Band Isoenzyme; mmHg – Millimeters of Mercury; mmol/L – Millimoles per Liter; g/L – Grams per Liter; ns – Not Significant; SD– Standard Deviation; IQR – Interquartile Range.

Preoperative echocardiographic and laboratory parameters confirmed severe AS, with a mean valve area of 0.71 cm^2 and a Vmax of 4.7 m/s. Baseline laboratory values are presented in Table 6.

Postoperatively, lactate and CK-MB decreased significantly from 6 to 24 hours, while hemoglobin increased. Oxygenation parameters remained stable, pH showed a slight but significant decrease, and no significant changes were observed in MAP, PaO_2, SaO_2, or $PaCO^2$ (Table 7).

The mean length of stay was 7 days, with most patients discharged on days 7–8. Only a few had shorter (5–6 days) or longer (9 days) hospitalizations (Figure 2).

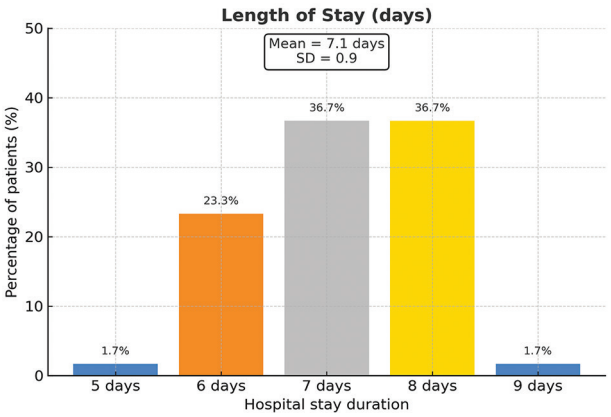


Figure 2. *Distribution of hospital stay (LOS) among patients, expressed in days (% of patients)*

Table 8. *Comparative overview of key studies in AS and LVH*

Study / Year	Focus	Key Findings	Relevance to Present Study
Généreux et al., 2017 [13]	AS staging	Proposed staging classification based on extent of cardiac damage	Validates LVH as prognostic marker
Bennett et al., 2024 [4]	LVH regression	Early regression of cell and matrix hypertrophy 2 months post-AVR	Similar regression trends observed
Mahmod et al., 2024 [5]	Remodeling differentiation	Differentiates AS vs hypertension-induced LVH	Supports interpretation of heterogeneous regression
Barletta et al., 2021 [6]	Long-term remodeling	LA recovery peaks at 3 months, LV recovery up to 2 years; high LVMI predicts residual hypertrophy	Highlights prognostic role of baseline LVMI
Khuong et al., 2023 [10]	Troponin & TAVR	Elevated troponin predicts adverse outcomes	Corroborates biomarker findings
Jakobsson et al., 2019 [12]	Oxygen consumption	General anesthesia reduces VO_2; perioperative oxygen balance critical	Supports perioperative findings
Jørgensen et al., 2024 [15]	NOTION-2 trial	TAVR effective in low-risk AS patients	Provides benchmark against surgical AVR
Leon et al., 2010 [16]	Inoperable AS	TAVR improved survival vs medical therapy	Contextualizes surgical AVR vs TAVR

DISCUSSION

Our findings reinforce the concept that aortic stenosis (AS) is not only a valvular disease but a systemic disorder involving ventricular remodeling and vascular adaptation (1, 3). Preoperatively, patients exhibited marked left ventricular hypertrophy (LVH), consistent with previous imaging-based studies (4, 5). Postoperatively, early metabolic improvement was evident, including decreased lactate and CK-MB levels and improved hemoglobin, supporting effective perioperative management and myocardial recovery (9, 10).

LVH regression after aortic valve replacement (AVR) remains heterogeneous. Some studies demonstrate partial reverse remodeling within two months (4), while others indicate that asymmetric septal hypertrophy requires longer recovery trajectories. Specifically, left atrial reverse remodeling peaks at three months, whereas maximal left ventricular recovery may take up to two years. Importantly, a higher preoperative left ventricular mass index (LVMI) has been associated with residual hypertrophy and adverse long-term outcomes (6).

Imaging continues to play a central role in evaluation and follow-up. Echocardiography reliably defines severity and monitors regression (7), while computed tomography (CT) provides critical information for operative and transcatheter aortic valve replacement (TAVR) planning (7). Cardiovascular magnetic resonance (CMR) adds unique insights into myocardial fibrosis and extracellular remodeling (8). Together, multimodality imaging allows individualized treatment planning and risk stratification.

Biomarker dynamics further complement imaging. In this study, early postoperative reductions in lactate and CK-MB were observed, paralleling previous reports of improving oxygen utilization and myocardial stabilization after AVR (9, 10). Troponin and multimarker panels have also been shown to predict adverse outcomes in both surgical and TAVR settings

(10), underscoring the role of perioperative biochemical surveillance.

The balance between oxygen delivery and consumption remains critical in elderly surgical patients with AS, particularly during cardiopulmonary bypass (11, 12). Our findings of a modest pH decline with otherwise stable oxygenation indices are consistent with earlier reports showing that myocardial injury risk is linked more to metabolic stress than to oxygen desaturation (11).

From a therapeutic perspective, both surgical AVR and TAVR continue to evolve. Surgical AVR in our series demonstrated low-to-moderate complication rates and a consistent median length of stay of seven days, reflecting outcomes comparable to contemporary surgical series. TAVR trials, including NOTION-2 and landmark studies by Leon et al., confirm excellent outcomes in low-risk and inoperable patients, respectively (15, 16). By contrast, all patients in our study underwent surgical AVR at a single center. Nevertheless, frailty and cerebral perfusion remain significant predictors of poor prognosis (13, 14).

Our data support integrating biomarkers, imaging, and LVH dynamics into decision-making to optimize patient selection and timing. A comparative overview of selected landmark studies is provided in Table 8.

Taken together, this study supports an integrated approach to severe AS, combining imaging, biomarkers, and careful assessment of LVH burden. Hemodynamic stability and metabolic recovery after surgery are reassuring early endpoints, but long-term outcomes will depend on the degree of LV regression and remodeling. Future multicenter studies with standardized imaging and extended follow-up are needed to confirm the prognostic role of early postoperative biomarker trends and to establish their relationship with ventricular remodeling and clinical outcomes.

CONCLUSION

Aortic stenosis is increasingly recognized as a systemic disorder involving valvular, ventricular, and vascular components. Our findings confirm that perioperative metabolic changes, biomarker fluctuations, and left ventricular hypertrophy significantly influence early postoperative outcomes after surgical valve replacement. While partial regression of hypertrophy is achievable, recovery remains incomplete in the early phase. These results support the growing shift toward earlier and individualized intervention, guided by an integrated approach combining imaging and biomarker assessment. Larger multicenter studies with standardized imaging and longer follow-up are warranted to validate these findings and to link early postoperative metabolic recovery with long-term ventricular remodeling and clinical outcomes.

Abbreviations

AF – atrial fibrillation
ASA – American Society of Anesthesiologists
AS – aortic stenosis
AVR – aortic valve replacement
BMI – body mass index
CK-MB – creatine kinase–MB isoenzyme
CPB – cardiopulmonary bypass
Hb – hemoglobin
Hct – hematocrit
IQR – interquartile range
LOS – length of stay
LVH – left ventricular hypertrophy
MAP – mean arterial pressure
$PaCO_2$ – arterial partial pressure of carbon dioxide
PaO_2 – arterial partial pressure of oxygen
SaO_2 – arterial oxygen saturation
SD – standard deviation
TAVR – transcatheter aortic valve replacement
Vmax – peak velocity

Ethics statement: The study was approved by the Institutional Ethics Committee of Acibadem-Sistina Hospital, Skopje, North Macedonia, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients prior to inclusion in the study.

Financial Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest Statement: The authors declare that there is no conflict of interest related to this paper.

Author Contribution & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. **Author Contribution: DS** – study conception and design, data collection; **DLS** – data interpretation, critical revision; **AGB** – clinical data analysis, manuscript editing; **MB** – perioperative management supervision; **HS** – manuscript drafting, literature review; **MJS** – statistical analysis, manuscript revision.

Data Availability Statement: Requests to access the datasets should be directed to the corresponding author.

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

Sažetak

PROCENA HEMODINAMSKIH I BIOMARKERSKIH PROMENA KOD PACIJENATA PODVRGNUTIH HIRURŠKOJ ZAMENI AORTNOG ZALISKA

Slaveski Dimce,[1] Lončar-Stojiljković Dragana,[1, 2] Gavrilovska Brzanov Aleksandra,[3, 4] Bozhinovska Marija,[5] Sulejmani Haris,[4] Jovanovski Srceva Marija[3, 4]

[1] Univerzitet u Banja Luci, Medicinski fakultet, Banja Luka, Bosna i Hercegovina
[2] Institut za kardiovaskularne bolesti Dedinje, Beograd, Srbija
[3] Univerzitetska klinika za traumatologiju, ortopedske bolesti, anesteziologiju, reanimaciju i intenzivnu negu i urgentnu medicinu, Skoplje, Severna Makedonija
[4] Univerzitet Sv Ćiril i Metodije u Skoplju, Medicinski fakultet, Skoplje, Severna Makedonija
[5] Univerzitetski medicinski centar Ljubljana, Klinika za anesteziologiju i perioperativnu intenzivnu terapiju, Ljubljana, Slovenija

Uvod: Aortna stenoza (AS) predstavlja sistemsku bolest koju karakterišu valvularna opstrukcija, ventrikularno remodelovanje i perioperativna osetljivost na disbalans između snabdevanja i potrošnje kiseonika. Cilj ove studije bio je da proceni perioperativne metaboličke i biomarkerske promene, kao i rane postoperativne ishode kod pacijenata podvrgnutih hirurškoj zameni aortnog zaliska (AVR).

Pacijenti i Metode: Sprovedena je prospektivna opservaciona studija na 60 uzastopnih odraslih pacijenata sa teškom aortnom stenozom (AS) koji su podvrgnuti hirurškoj zameni aortnog zaliska (AVR) u jednoj ustanovi. Analizirani su demografski i antropometrijski podaci, intraoperativni parametri, postoperativne komplikacije, kao i hemodinamski i laboratorijski pokazatelji pre i posle operacije.

Postoperativno su, nakon 6 i 24 časa, praćeni sledeći parametri: srednji arterijski pritisak (MAP), arterijska saturacija kiseonikom (SaO_2), parcijalni pritisak kiseonika (PaO_2), pH, parcijalni pritisak ugljen-dioksida ($PaCO_2$), hemoglobin (Hb), laktat i kreatin kinaza–MB izoenzim (CK-MB). Kontinuirane vrednosti prikazane su kao srednja vrednost ± standardna devijacija (SD) ili kao medijana (interkvartilni opseg, IQR). Za poređenje vrednosti između 6. i 24. časa korišćen je parni t-test.

Rezultati: Prosečna starost pacijenata iznosila je 69,9 ± 7,3 godine; 58,3% bili su muškarci. Prosečno trajanje anestezije i operacije bilo je 151,5 ± 21,8, odnosno 126,8 ± 20,6 minuta, dok su prosečna vremena na kardiopulmonalnom bajpasu (CPB) i klemovanja iznosila 78,3 ± 17,6 i 58,5 ± 16,7 minuta.

Gotovo polovina pacijenata (46,7%) nije imala postoperativne komplikacije, dok su kod ostalih zabeležene sledeće: krvarenje (16,7%), aritmije koje su zahtevale terapiju (6,7%), ugradnja trajnog pejsmejkera (8,3%), reintervencija (6,7%), infekcija (8,3%), respiratorna insuficijencija (3,3%) i bubrežna insuficijencija (3,3%).

Od 6. do 24. časa postoperativno, vrednosti laktata su se smanjile (2,34 ± 0,96 → 1,87 ± 0,98 mmol/L; p = 0,006), CK-MB se smanjio (52,5 ± 34,2 → 39,0 ± 30,8 U/L; p = 0,001), dok je hemoglobin porastao (103,5 ± 10,1 → 120,1 ± 22,9 g/L; p < 0,001). pH se blago smanjio (7,396 ± 0,057 → 7,365 ± 0,065; p = 0,015). MAP, SaO_2, PaO_2 i $PaCO_2$ nisu pokazali statistički značajne promene. Medijana dužine hospitalizacije iznosila je 7 dana (IQR 6–8).

Zaključak: Kod pacijenata podvrgnutih hirurškoj zameni aortnog zaliska zbog aortne stenoze, rani postoperativni trendovi ukazuju na poboljšanje metaboličkog profila (niže vrednosti laktata) i normalizaciju biomarkera (CK-MB) uz stabilnu oksigenaciju, kao i nisku do umerenu stopu komplikacija i konstantnu medijanu hospitalizacije od sedam dana. Integrisanje perioperativnih markera balansa kiseonika i srčanih biomarkera sa imidžing metodama i procenom hipertrofije leve komore (LVH) može doprineti preciznijem određivanju vremena i stratifikaciji rizika za intervenciju. Potrebne su prospektivne studije sa standardizovanim imidžing metodama i dužim praćenjem kako bi se potvrdila povezanost rane metaboličke stabilizacije sa remodelovanjem leve komore i kliničkim ishodima.

Ključne reči: aortna stenoza, zamena aortnog zaliska, laktat, kreatin kinaza–MB izoenzim, biomarkeri.

REFERNCES

1. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022; 43(7): 561-632. doi: 10.1093/eurheartj/ehab395.

2. Bakaeen FG, Rosengart TK, Carabello BA. Aortic stenosis. Ann Intern Med. 2017; 166(1): ITC1-16. doi: 10.7326/AITC201701030.

3. Bäck M, Marie PY. Valve, ventricle, and vessel: the triumvirate of aortic stenosis assessment. Circ Cardiovasc Imaging. 2016; 9(3): e004590. doi: 10.1161/CIRCIMAGING.116.004590.

4. Bennett J, Thornton GD, Nitsche C, Gama FF, Aziminia N, Gul U, et al. Left ventricular hypertrophy in aortic stenosis: early cell and matrix regression 2 months post-aortic valve replacement. Circ Cardiovasc Imaging. 2024; 17(12): e017425. doi: 10.1161/CIRCIMAGING.124.017425.

5. Mahmod M, Chan K, Fernandes JF, Ariga R, Raman B, Zacur E, et al. Differentiating left ventricular remodeling in aortic stenosis from systemic hypertension. Circ Cardiovasc Imaging. 2024; 17(8): e016489. doi: 10.1161/CIRCIMAGING.123.016489.

6. Barletta G, Del Bene MR, Venditti F, Pilato G, Stefàno P. Surgical aortic valve replacement and left ventricular remodeling: survival and sex-related differences. Echocardiography. 2021; 38(7): 1095-103. doi:10.1111/echo.15122.

7. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2017; 30(4): 372-92. doi: 10.1016/j.echo.2017.02.009.

8. Mahon C, Mohiaddin RH. The emerging applications of cardiovascular magnetic resonance imaging in transcatheter aortic valve implantation. Clin Radiol. 2021; 76(1): 73.e21-73.e37. doi: 10.1016/j.crad.2019.11.011.

9. Charitakis K, Nguyen TC. Severe symptomatic aortic stenosis? Check troponin, too. J Am Heart Assoc. 2019; 8(6): e012156. doi: 10.1161/JAHA.119.012156.

10. Khuong JN, Liu Z, Campbell R, Jackson SM, Borg Caruana C, Ramson DM, et al Troponin as a predictor of outcomes in transcatheter aortic valve implantation: systematic review and meta-analysis. Gen Thorac Cardiovasc Surg. 2023; 71(1): 12-19. doi: 10.1007/s11748-022-01888-2.

11. Jakobsson J, Vadman S, Hagel E, Kalman S, Bartha E. The effects of general anaesthesia on oxygen consumption: A meta-analysis guiding future studies on perioperative oxygen transport. Acta Anaesthesiol Scand. 2019; 63(2): 144-153. doi: 10.1111/aas.13265.

12. Lugo G, Arizpe D, Domínguez G, Ramírez M, Tamariz O. Relationship between oxygen consumption and oxygen delivery during anesthesia in high-risk surgical patients. Crit Care Med. 1993; 21(1): 64-9. doi: 10.1097/00003246-199301000-00014.

13. Généreux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, et al. Staging classification of aortic stenosis based on cardiac damage. Eur Heart J. 2017; 38(45): 3351-8. doi: 10.1093/eurheartj/ehx381.

14. Généreux P, Pibarot P, Redfors B, Bax JJ, Zhao Y, Makkar RR, et al. Evolution and prognostic impact of cardiac damage after aortic valve replacement. J Am Coll Cardiol. 2022; 80(8): 783-800. doi: 10.1016/j.jacc.2022.05.006.

15. Jørgensen TH, Thyregod HGH, Savontaus M, Willemen Y, Bleie Ø, Tang M, et al. Transcatheter aortic valve implantation in low-risk tricuspid or bicuspid aortic stenosis: the NOTION-2 trial. Eur Heart J. 2024; 45(37): 3804-14. doi: 10.1093/eurheartj/ehae331.

16. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010; 363(17): 1597-607. doi: 10.1056/NEJMoa1008232.

Correspondence to/Autor za korespondenciju
Haris Sulejmani
Faculty of Medicine, Ss. Cyril and Methodius University, Skopje,
Republic of North Macedonia
50 Division, number 6, 1000 Skopje
e-mail: sulejmani.haris@hotmail.com
tel. +38971986840

ORCID IDs:
Haris Sulejmani 0009-0002-5583-5489
Dimce Slaveski 0000-0001-5610-9679
Dragana Lončar-Stojiljković 0000-0003-4875-3952
Aleksandra Gavrilovska Brzanov 0000-0001-9593-2502
Bozhinovska Marija 0000-0003-4951-1496
Marija Jovanovski Srceva 0000-0002-3105-0081

***How to cite this article**:* Slaveski D, Lončar-Stojiljković D, Gavrilovska Brzanov A, Bozhinovska M, Sulejmani H, Jovanovski Srceva M. Evaluation of Hemodynamic and Biomarker Changes in Patients Undergoing Surgical Aortic Valve Replacement. Sanamed. 2025; 20(3): 259-267. doi: 10.5937/sanamed0-61650.

SANAMED
2025; 20(3): 269–274
ISSN-1452-662X

DOI: 10.5937/sanamed0-62248
UDK: 616.132-005.6
ID: 183787529
Case report

AORTIC AND SUPERIOR MESENTERIC ARTERY THROMBOSIS IN ANTITHROMBIN III DEFICIENCY-DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN CONSERVATIVE MANAGEMENT

Surla Dimitrije,[1] Nikolić Marija,[1] Trifunović Nemanja,[1] Stojadinović Milica[2]

[1] Clinical Hospital Center Zemun, Department of general surgery, Belgrade, Serbia
[2] University Clinical Center of Serbia, Center for Radiology and Magnetic Resonance, Belgrade, Serbia

Primljen/Received: 18. 10. 2025. Prihvaćen/Accepted: 26. 11. 2025. Online First: 28. 11. 2025.

Abstract: **Introduction:** Thrombosis of large arterial vessels, such as the abdominal aorta and superior mesenteric artery, is a rare but serious condition that requires timely diagnosis and appropriate management. One of the risk factors is antithrombin III (AT III) deficiency, a rare coagulation disorder that increases the likelihood of thrombosis. While arterial thromboses are less common than venous ones, they can have significant clinical consequences.

Case report: We present the case of a 39-year-old woman hospitalized due to sudden abdominal pain. Diagnostic imaging, including a contrast-enhanced CT scan of the abdomen and pelvis and CT angiography, revealed thrombosis of the distal abdominal aorta and superior mesenteric artery. Laboratory testing confirmed low AT III levels, while tests for hereditary thrombophilias were negative, suggesting a likely acquired deficiency.

The patient was treated conservatively with AT III concentrate, low-molecular-weight heparin, and oral anticoagulation. Therapy was complemented with cardioprotective and gastroprotective medications, as well as physical rehabilitation. During hospitalization, the patient remained hemodynamically stable, and symptoms gradually resolved. Follow-up imaging after several months demonstrated complete recanalization of the affected vessels. Long-term monitoring over two years confirmed stable clinical status and absence of recurrent thrombosis.

Conclusion: This case highlights the importance of early diagnosis, identification of the underlying cause, and carefully implemented conservative management in patients with AT III deficiency. It demonstrates that even in extensive arterial thrombosis, conservative management can preserve organ function and achieve a favorable outcome without the need for surgical intervention.

Keywords: abdominal aorta thrombosis, superior mesenteric artery thrombosis, antithrombin III deficiency, conservative treatment, anticoagulation therapy.

INTRODUCTION

Thrombosis of large arterial vessels, particularly the abdominal aorta and mesenteric arteries, represents a rare but potentially life-threatening condition that requires urgent diagnosis and a coordinated multidisciplinary therapeutic approach. In elderly patients, the most common causes include atherosclerosis, aneurysmal changes, or cardiogenic sources of embolism, whereas in younger individuals such manifestations are often associated with congenital or acquired coagulation disorders. Although rare, antithrombin III deficiency significantly increases the risk of thromboembolic events, with venous thromboses being far more common. Arterial thromboses, though less frequent, represent a serious clinical challenge with potentially severe outcomes. Timely recognition of such conditions, supported by detailed laboratory and radiological diagnostics, is crucial for therapeutic planning and prevention of complications (1, 2).

The presented case describes a young female patient with extensive thrombosis of the abdominal aorta and superior mesenteric artery. The aim of this report is to emphasize the importance of early diagnosis, precise determination of the etiology of thrombosis, and an effective conservative therapeutic approach, which in this case enabled preservation of vital organ function and achievement of a favorable long-term outcome.

CASE PRESENTATION

A 39-year-old female patient was admitted to the Department of General Surgery on April 10, 2022, due to the sudden onset of severe abdominal pain. Upon admission, she was conscious, communicative, afebrile, and hemodynamically stable, with normal vital parameters. Her medical history was unremarkable, with no chronic illnesses, previous surgeries, or similar symptoms reported.

A contrast-enhanced CT scan of the abdomen and pelvis revealed thrombotic material in the distal portion of the abdominal aorta extending into the superior mesenteric artery (SMA), with signs of reduced perfusion in certain segments of the small intestine but without evidence of perforation or ileus. No pathological changes were observed in the parenchymal abdominal organs (Figure 1 and 2).

CT angiography confirmed thrombosis of the distal abdominal aorta and superior mesenteric artery. According to the initial radiology report, subocclusive changes of several distal branches in the lower extremities were described. However, since the original images are unavailable, these findings could not be independently verified.

A follow-up abdominal CT scan performed on April 12, 2022, confirmed the presence of the abdominal thrombosis without progression or signs of acute complications. A moderate amount of free fluid was noted, without signs of peritonitis.

Laboratory analyses revealed a decreased level of antithrombin III, leading to the initiation of therapy with antithrombin concentrate (Kybernin). In the initial phase, anticoagulant therapy with low-molecular-weight heparin was administered, followed by a transition to oral anticoagulant therapy (rivaroxaban). The therapeutic protocol also included cardioprotective medication (acetylsalicylic acid), gastroprotective therapy, and symptomatic analgesia.

During hospitalization, the patient remained hemodynamically stable, without signs of progression of abdominal symptoms. She repeatedly complained of pain and weakness in the right foot; clinical examination confirmed limited dorsiflexion. Physical therapy was initiated to preserve muscle strength and function, resulting in gradual clinical improvement.

The patient was discharged on April 21, 2022, in good general condition, afebrile, and with a normal abdominal examination. Continued anticoagulant therapy, regular hematologic follow-up due to suspected coagulation disorder, and ongoing supervision by a vascular surgeon and physiatrist were recommended.

At a follow-up examination in September 2022, CT angiography demonstrated complete revascularization. The patient still reported a subjective burning sensation in the right leg but had no new symptoms or signs of acute ischemia. Continuation of the current therapy for an additional two months was advised, followed by re-evaluation.

***Figure 1**. CT aortography demonstrating thrombotic occlusion of the abdominal aorta extending into the superior mesenteric artery (SMA). The arrow indicates an intraluminal filling defect corresponding to acute thrombus formation. Absence of contrast opacification distal to the thrombus is consistent with complete arterial occlusion.*
(The image is from the authors'archive.)

***Figure 2.** Follow-up abdominal CT performed two days after admission demonstrates the presence of thrombotic masses, with no evidence of progression compared to the previous study and preserved viability of intra-abdominal organs.*
(The image is from the authors' archive.)

In addition to the above investigations, genetic testing for hereditary thrombophilias (Factor V Leiden, prothrombin G20210A mutation, MTHFR, and PAI-1) was performed, all yielding negative results.

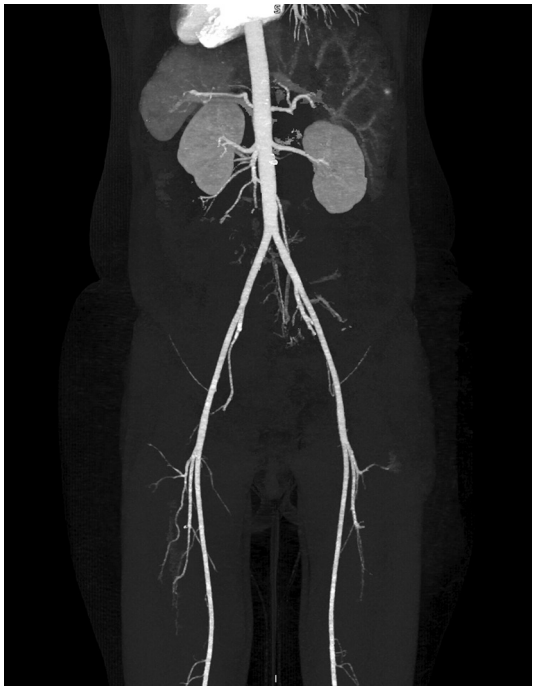


Figure 3. *Follow-up CT aortoarteriography after two years demonstrates complete recanalization of all abdominal and lower extremity vessels. (The image is from the authors' archive)*

The patient was subsequently followed regularly over the next two years, with normal laboratory findings, including antithrombin III levels, and without any recurrence of thromboembolic events (Figure 3).

DISCUSSION

Antithrombin III (AT III) deficiency is a rare but clinically significant disorder of hemostasis that increases the risk of thromboembolic events (3). Congenital forms usually manifest at a younger age, whereas acquired forms are more commonly observed in the context of acute thrombotic episodes, liver disease, nephrotic syndrome, or disseminated intravascular coagulation (DIC) (4, 5, 6).

In our patient, AT III deficiency was detected during an episode of acute thrombosis of the abdominal aorta and mesenteric artery. Genetic testing for hereditary thrombophilias (Factor V Leiden, prothrombin G20210A mutation, MTHFR, and PAI-1) was negative, suggesting a likely acquired rather than congenital form of the disorder. During a two-year follow-up period, AT III levels were regularly monitored and consistently within the reference range. These findings indicate that the condition was not a classical hereditary thrombophilia, suggesting either an acquired deficiency or a rare congenital form undetectable by standard genetic panels.

Regardless of etiology, the negative thrombophilia results and stable AT III levels highlight the importance of continuous hematologic monitoring and an individualized anticoagulant regimen, which reduced the risk of thrombotic recurrence and contributed to a favorable long-term outcome.

Arterial thrombosis of the abdominal aorta and mesenteric arteries is rare in younger individuals and is typically associated with atherosclerosis, cardioembolic sources, or coagulation disorders (5, 6, 7). In this case, the sudden onset of abdominal pain combined with findings from CT angiography enabled early diagnosis and initiation of targeted therapy. Despite extensive thrombotic involvement, the patient was managed conservatively with administration of antithrombin concentrate, low-molecular-weight heparin, and subsequent transition to rivaroxaban. Activated partial thromboplastin time, thrombin time, prothrombin time, anti-Xa activity, and D-dimer levels were regularly monitored.

This approach led to clinical stabilization, symptom regression, and complete vascular recanalization confirmed by follow-up CT angiography. The significance of this case lies in the successful conservative therapeutic approach, which effectively controlled the thrombotic process without the need for surgical intervention. The combination of antithrombin replacement, anticoagulant therapy, and close coagulation profile monitoring represents a standardized and safer treatment strategy for patients with AT III deficiency and multiple arterial thromboses, particularly in those with hemodynamic stability and no signs of acute ischemia of vital organs (1, 3, 6, 8). This approach allows gradual thrombus resolution, vascular lumen recanalization, and reduction of complications such as intestinal or limb infarction.

At the same time, multidisciplinary management involving a hematologist, vascular surgeon, and physiatrist ensures optimal coagulation control, neuromuscular function monitoring, and timely intervention in case of clinical deterioration. It is noteworthy that, despite initial neuromuscular symptoms affecting the right foot, the patient achieved good functional recovery with appropriate physical therapy. Long-term follow-up over two years demonstrated the absence of recurrent thrombosis and normal laboratory findings, confirming the efficacy of the conservative approach in this case.

This case highlights the importance of early diagnosis, individualized treatment planning, and multidisciplinary supervision in patients with suspected coagulation disorders. It also demonstrates that even extensive arterial thromboses can be successfully managed conservatively when therapy is carefully implemented and patients are closely monitored, thereby avoiding surgical intervention.

Table 1. *Conservative Therapy of Arterial Thrombosis in Antithrombin III Deficiency*

Therapy / Medication	Dosage / Administration	Duration	Notes / Purpose
Kybernin (Antithrombin III concentrate)	Individually adjusted dose according to AT III level	During the acute phase of hospitalization	Replacement of antithrombin III deficiency and stabilization of coagulation
Low-Molecular-Weight Heparin (LMWH)	Subcutaneous, therapeutic dose based on body weight	Initial phase of hospitalization	Rapid anticoagulation and prevention of thrombus progression
Oral anticoagulant	Initial dose titrated according to coagulation profile values	Long-term, per hematologic supervision	Maintenance of therapeutic dose and prevention of thrombotic recurrence
Acetylsalicylic Acid (ASA)	Standard cardioprotective dose (75–100 mg daily)	Long-term	Additional antithrombotic protection and cardioprotection
Gastroprotective therapy (PPI)	Standard dose	As needed with ASA / anticoagulants	Prevention of gastrointestinal complications
Analgesics	As needed	Symptomatic	Pain control
Physical therapy	Individual exercise program for the lower extremity	During and after hospitalization	Preservation of muscle strength and foot function, rehabilitation

Table 1 was created based on data synthesized from references (2, 3, 7, 9, 10, 11).

Table 2. *Surgical and Endovascular Treatment of Arterial Thrombosis: Indications and Methods*

Type of Intervention	Indications	Methods / Procedures	Notes / Objective
Conventional (Open) Surgery	- Acute ischemia of vital organs or limbs - Failure of conservative or endovascular therapy - Extensive or multiple thromboses - Anatomical obstacles preventing endovascular access	- Thrombectomy - Endarterectomy - Bypass procedures	Direct arterial recanalization, restoration of perfusion, and achievement of long-term vascular patency; associated with higher surgical risk and longer recovery period
Endovascular Procedures (Minimally Invasive)	- Subacute or acute thrombosis with preserved hemodynamic stability - High surgical risk - Partial thrombosis or segments accessible via catheter	- Catheterdirected thrombolysis - Percutaneous thrombectomy - Stent placement	Minimally invasive; reduce hospitalization time; often combined with anticoagulant therapy; suitable for patients with multiple or partially accessible arterial thromboses

Table 2 was created based on clinical concepts and therapeutic principles described in references (7, 8, 11).

Although conservative treatment was successful in this case, surgical management remains an important option for patients presenting with signs of acute ischemia of vital organs or limbs, progressive thrombosis, or failure of conservative therapy. Indications for surgery include acute intestinal infarction, limb gangrene, massive thrombosis compromising hemodynamic stability, or the presence of embolic fragments posing a risk of distal arterial occlusion. Surgical approaches may include thrombectomy, endarterectomy, bypass grafting, or other reconstructive vascular procedures, depending on the localization and extent of thrombosis (9, 10). Decision-making regarding surgical intervention requires a multidisciplinary assessment involving vascular surgeons, hematologists, and radiologists to evaluate risk–benefit ratios and determine the optimal timing of surgery.

Literature reports indicate that, when feasible, an early combination of anticoagulant therapy and selective surgical intervention can improve outcomes and reduce morbidity, especially in patients with extensive or multiple arterial thromboses (Table 1).

In recent decades, endovascular procedures have emerged as an important alternative to open surgery in the treatment of arterial thromboses, particularly in patients with high surgical risk or limited resectable segments. Techniques such as catheter-directed thrombolysis, percutaneous thrombectomy, and stent placement enable direct thrombus dissolution or removal, restoration of perfusion, and reduction of long-term tissue damage. Endovascular approaches are typically used in subacute or acute thromboses where there is a vital threat to an organ or limb but hemodynamic stability can be maintained. These minimally invasive methods, often combined with systemic or local anticoagulant therapy, enhance treatment efficacy and reduce the need for open surgical procedures (1, 5, 9) (Table 2).

According to the literature, timely application of endovascular interventions can significantly improve outcomes, shorten hospitalization, and decrease morbidity in patients with extensive arterial thromboses (11).

CONCLUSION

The presented case demonstrates that antithrombin III deficiency, although rare, can lead to extensive arterial thrombosis and severe clinical manifestations even in younger patients. Timely diagnosis and implementation of a conservative therapeutic approach resulted in a favorable outcome without the need for surgical intervention. Long-term follow-up confirmed clinical stability and absence of recurrence, emphasizing the importance of early recognition and appropriate management of such coagulation disorders.

Financial Support: This research received no external funding or sponsorship.

Conflict of Interest Statement: The authors declare that there is no conflict of interest related to this paper.

Author Contribution & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript.

Authors' contributions: **SD**: conceptualization, methodology, data curation, investigation, project administration, writing – original draft; **NM**: conceptualization, methodology, project administration, supervision, writing – original draft; **TN**: formal analysis, writing – original draft, writing – review and editing; **SM:** validation, methodology, investigation, writing – review and editing.

Data Availability Statement: Requests to access the datasets should be directed to the corresponding author.

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

Sažetak

TROMBOZA AORTE I GORNJE MEZENTERIJALNE ARTERIJE U SKLOPU DEFICITA ANTITROMBINA III-DIJAGNOSTIČKI I TERAPIJSKI IZAZOVI KONZERVATIVNOG LEČENJA

Surla Dimitrije,[1] Nikolić Marija,[1] Trifunović Nemanja,[1] Stojadinović Milica[2]

[1] Kliničko bolnički centar Zemun, Služba opšte hirurgije, Beograd, Srbija
[2] Univerzitetski klinički centar Srbije, Centar za radiologiju i magnetnu rezonancu, Beograd, Srbija

Uvod:Tromboza velikih arterijskih krvnih sudova, kao što su abdominalna aorta i gornja mezenterijalna arterija, predstavlja retko, ali ozbiljno stanje koje zahteva pravovremenu dijagnostiku i adekvatan terapijski pristup. Jedan od faktora rizika je deficit antitrombina III (AT III), redak poremećaj koagulacije koji povećava verovatnoću nastanka tromboza, pri čemu su arterijske tromboze ređe, ali potencijalno ozbiljnije.

Prikaz slučaja: Predstavljamo slučaj 39-godišnje žene koja je hospitalizovana zbog naglog abdominalnog bola. Dijagnostika, uključujući CT abdomena i male karlice i CT angiografiju, otkrila je trombozu distalnog dela abdominalne aorte i gornje mezenterijalne arterije. Laboratorijskim testom potvrđen je nizak nivo AT III, dok su testovi na nasledne trombofilije bili negativni, sugerišući verovatnost stečenog oblika deficita.

Pacijentkinja je lečena konzervativno, uz primenu koncentrata antitrombina, niskomolekularnog heparina i oralnog antikoagulanta. Terapija je dopunjena kardioprotektivnim i gastroprotektivnim lekovima, kao i fizikalnom rehabilitacijom. Tokom hospitalizacije stanje pacijentkinje bilo je stabilno, a simptomi su se

postepeno povukli. Kontrolna dijagnostika nakon nekoliko meseci pokazala je potpunu rekanalizaciju zahvaćenih krvnih sudova, a dugoročno praćenje tokom dve godine potvrdilo je stabilnost kliničkog stanja i odsustvo recidiva tromboze.

Zaključak: Ovaj slučaj ističe važnost rane dijagnostike, identifikacije uzroka tromboze i pažljivo sprovedenog konzervativnog lečenja kod pacijenata sa deficitom AT III. Pokazuje da, i kod opsežnih arterijskih tromboza, takav pristup može obezbediti očuvanje funkcije organa i povoljan ishod bez potrebe za hirurškom intervencijom.

Ključne reči: tromboza abdominalne aorte, tromboza gornje mezenterijalne arterije, deficit antitrombina III, konzervativno lečenje, antikoagulantna terapija.

REFERENCES

1. Gindele R, Selmeczi A, Oláh Z, Ilonczai P, Pfliegler G, Marján E, et al. Clinical and laboratory characteristics of antithrombin deficiencies: a large cohort study from a single diagnostic center. Thromb Res. 2017; 160: 119–128. doi: 10.1016/j.thromres.2017.10.023.

2. Corral J, Vicente V. Puzzling questions on antithrombin: diagnostic limitations and real incidence in venous and arterial thrombosis. Thromb Res. 2015; 135(6): 1047–8. doi: 10.1016/j.thromres.2015.04.012.

3. Schwartz RS, Bauer KA, Rosenberg RD, Kavanaugh EJ, Davies DC, Bogdanoff DA. Clinical experience with antithrombin III concentrate in treatment of congenital and acquired deficiency of antithrombin. The Antithrombin III Study Group.. Am J Med. 1989; 87(3B): 53S–60S. doi: 10.1016/0002-9343(89)80533-9.

4. Roberts JC, von Drygalski A, Zhou JY, Rodgers GM, Ansteatt K, Tarantino MD. Five challenging cases of hereditary antithrombin deficiency characterized by thrombosis or complicated pregnancy. J Blood Med. 2022; 13: 611–8. doi: 10.2147/JBM.S365996.

5. Rojnik T, Sedlar N, Turk N, Kastrin A, Debeljak M, Božič Mijovski M. Comparison of antithrombin activity assays in detection of patients with heparin binding site antithrombin deficiency: systematic review and meta-analysis. Sci Rep. 2023; 13(1): 16734. doi: 10.1038/s41598-023-43941-x.

6. von Blohn G, Hellstern P, Köhler M, Scheffler P, Wenzel E. Clinical aspects of acquired antithrombin III deficiency. Behring Inst Mitt. 1986; (79): 200–15. German.

7. Ehrhardt JD Jr, Boneva D, McKenney M, Elkbuli A. Antithrombin deficiency in trauma and surgical critical care. J Surg Res. 2020; 256: 536–42. doi: 10.1016/j.jss.2020.07.010.

8. Farrell DH, McConnell KM, Zilberman-Rudenko J, Behrens B, Mcloud S, Cook MR, et al. Antithrombin III levels and outcomes among patients with trauma. JAMA Netw Open. 2024; 7(8): e2427786. doi: 10.1001/jamanetworkopen.2024.27786.

9. Tormene D, Noventa F, Campello E, Gavasso S, Marobin M, Turatti G, et al. The risk of arterial thrombosis in carriers of natural coagulation inhibitors: a prospective family cohort study. Intern Emerg Med. 2021; 16(4): 997–1003. doi: 10.1007/s11739-021-02656-5.

10. Englisch C, Königsbrügge O, Nopp S, Moik F, Quehenberger P, Preusser M, et al. Antithrombin activity and association with risk of thrombosis and mortality in patients with cancer. Int J Mol Sci. 2022; 23(24): 15770. doi: 10.3390/ijms232415770.

11. Rodgers GM, Mahajerin A. Antithrombin therapy: current state and future outlook. Clin Appl Thromb Hemost. 2023; 29: 10760296231205279. doi: 10.1177/10760296231205279.

Correspondence to/Autor za korespondenciju
Marija Nikolić, Vukova 9, Belgrade, Serbia
Email: marija.nikolic80@gmail.com
Phone: +381 64 413 9268

ORCID IDs
Marija Nikolić: 0009-0004-3415-1277
Nemanja Trifunović: 0009-0001-1085-9500

How to cite this article: **Surla D, Nikolić M, Trifunović N, Stojadinović M**. Aortic and superior mesenteric artery thrombosis in antithrombin III deficiency –diagnostic and therapeutic challenges in conservative management. Sanamed. 2025; 20(3): 269-274. doi: 10.5937/sanamed0-62248.

SANAMED
2025; 20(3): 275–279
ISSN-1452-662X

DOI: 10.5937/sanamed20-62340
UDK: 616-001.43-056.3:616.12
ID: 183832841
Case report

AN UNUSUAL PRESENTATION OF TYPE I KOUNIS SYNDROME: HIGH TROPONIN WITHOUT CHEST PAIN AFTER ANAPHYLAXIS

Čekić Said,[1, 2] Gutić Medo,[3] Milidrag Ardea[4]

[1] Emergency Medical Care Institute of Montenegro, Plav, Montenegro
[2] University of Travnik, Faculty of Pharmacy and Health, Travnik, Bosnia and Herzegovina
[3] Public Health Institution Health Center Dr Branko Zogović, Plav, Montenegro
[4] University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

Primljen/Received: 22. 10. 2025. Prihvaćen/Accepted: 13. 12. 2025.

Abstract: **Introduction:** Kounis syndrome is defined as the simultaneous occurrence of acute coronary syndrome and an allergic or anaphylactic reaction. It primarily affects men between 40 and 70 years of age and is often associated with chest pain. Owing to limited awareness, this syndrome is frequently under-recognized and under-diagnosed in clinical practice.

Case presentation: We report a case of type I Kounis syndrome in a young woman without chest pain. The patient, who had allergic asthma since childhood, developed anaphylactic shock during the administration of bronchodilators, corticosteroids, and an antibiotic in an emergency outpatient setting, followed by cardiac arrest. Subsequent laboratory testing confirmed acute coronary syndrome.

Conclusion: Although Kounis syndrome is uncommon, particularly in young women, clinicians should consider the possibility of acute coronary syndrome in severe allergic reactions. In this case, myocardial injury was documented by electrocardiographic changes and later by cardiac biomarkers consistent with coronary syndrome.

Keywords: allergic reaction, acute coronary syndrome, resuscitation.

INTRODUCTION

Kounis syndrome is defined as acute coronary syndrome (ACS) occurring simultaneously with an allergic or anaphylactic reaction, mediated by mast-cell activation and the release of inflammatory mediators and cytokines (1, 2). Three mechanistic types are recognized: type I, vasospastic ACS in angiographically normal coronaries without atherosclerosis; type II, ACS triggered by erosion or rupture of pre-existing atheromatous plaques; and type III, ACS in the presence of intracoronary stents, subclassified into IIIa (stent thrombosis) and IIIb (in-stent restenosis) (2, 3). Triggers include drugs, foods, and insect stings, which induce mast-cell degranulation with histamine, leukotrienes, prostaglandins, chymase, and related mediators that promote coronary vasoconstriction, platelet activation, and thrombosis, resulting in ACS (1, 2, 4). Limited clinical awareness leads to under-recognition and under-diagnosis in routine practice (5).

Epidemiological data indicate an occurrence of approximately 1.1–3.4% among patients with allergic manifestations (6, 7). Men are more frequently affected (~74%), the peak age ranges from 40 to 70 years (~68%), and chest pain is reported in ~87% of cases (8). We report a type I presentation in a 25-year-old woman without chest pain, illustrating a painless phenotype that may delay recognition.

CASE PRESENTATION

A 25-year-old female patient with allergic asthma since childhood, treated with fenoterol hydrobromide plus ipratropium bromide aerosols and, more recently, theophylline capsules, presented to the intensive care unit with chest wheezing, a choking sensation, and cough. On admission, her temperature was 36.8 °C, blood pressure 110/80 mmHg, peripheral oxygen saturation (SpO_2) 91% on room air, and pulse 85/min. Lung auscultation revealed prolonged expiration with diffuse wheezes. She denied chest pain. Family history was notable for maternal allergic asthma. She denied drug allergies. She reported frequent asthma attacks; the current attack began during the night, and she sought care in the intensive care unit at 09:30.

Treatment was initiated with intravenous infusion solutions, a systemic corticosteroid, an antihistamine,

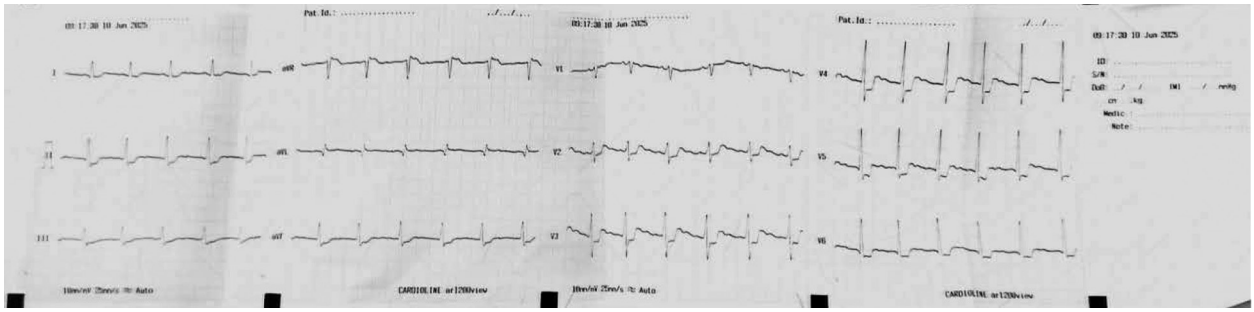


Figure 1. *ECG recording after resuscitation measure*

and bronchodilators. Initial subjective improvement was followed by rapid deterioration, with impaired consciousness and increasing respiratory difficulty, progressing to respiratory arrest with cardiac arrest and unmeasurable blood pressure. Cardiopulmonary resuscitation (CPR) was commenced, including administration of epinephrine, to which she responded. Return of spontaneous circulation was achieved, with restoration of spontaneous breathing and heart activity. She vomited several times and subsequently became communicicative, reporting headache as the predominant symptom. She continued to deny chest pain. A post-resuscitation electrocardiogram (ECG) demonstrated ST-segment depression in leads II, III, aVF, V2, V3, V4, V5, and V6, with ST-segment elevation in aVR (Figure 1).

The post-resuscitation ECG, in sinus rhythm at a rate of 120/min, shows marked ST-segment depression in leads II, III, aVF, and V2–V6, with ST-segment elevation in aVR. The patient reported no chest pain at the time of recording.

The patient was transported to a higher-level health facility hemodynamically stable, with normal vital parameters. Laboratory results on admission were as follows: troponin I 512 pg/mL (reference 29.62–74.64 pg/mL), D-dimer 2.86 mg/L FEU (reference 0–0.55 mg/L FEU), leukocytes 14.10 × 10^9/L (reference 3.9–10.0 × 10^9/L), and prothrombin time 13.5 s (reference 9.3–11.6 s) (Table 1 and 2).

The leukocyte count was elevated above the reference range, supporting an inflammatory component in the overall clinical picture. In anaphylactic reactions, generalized vasomotor disturbances and complex pathophysiological mechanisms can affect coagulation; accordingly, the findings included mildly prolonged prothrombin time and elevated D-dimer values.

The next day, troponin I was 1264.15 pg/mL (reference 29.62–74.64 pg/mL). On 09/09/2025, four days after the anaphylactic shock, the findings were as follows: leukocytes 14.00 × 10^9/L, D-dimer 0.87 mg/L FEU, troponin I 108.11 pg/mL, and BNP 31.80 pmol/L (reference 0–28.9 pmol/L).

During hospitalization, transthoracic echocardiography was performed, and no segmental wall-motion abnormalities were observed.

Table 1. *Troponin values*

Troponin values			
Day	Hour	Result	Reference value
05.09.2025	11.41	512.92 pg/ml	29.62-74.64 pg/ml
05.09.2025	14.29	1117.64 pg/ml	29.62-74.64 pg/ml
05.09.2025	19.35	1545.44 pg/ml	29.62-74.64 pg/ml
06.09.2025	06.26	1264.15 pg/ml	29.62-74.64 pg/ml
09.09.2025	06.28	108.11 pg/ml	29.62-74.64 pg/ml
11.09.2025	06.31	34.7 pg/ml	29.62-74.64 pg/ml

Table 2. *Additional Laboratory Findings*

Other laboratory analysis				
Date	Hour	Analysis	Result	Reference value
05.11.2025	14:35	Leukocites	19x10^9/L	3.9 - 10x10^9/L
05.11.2025	14:35	Prothrombin time	13.1 s	9,3-11,6 s
05.11.2025	14:35	D - dimer	2,21mg/L FEL	0-0,55 mg/LFEL

DISCUSSION

Symptoms of myocardial ischemia and infarction in Kounis syndrome exhibit sex-related differences, with women reporting chest pain less frequently than men (9-17). Although the mechanisms underlying sex differences in the presentation of coronary artery disease are incompletely defined, estrogen has been implicated in the modulation of pain sensitivity and nociceptive processing (18–21). The absence of chest pain at presentation in the current case may therefore be related, at least in part, to female sex. Kounis syndrome is most frequently reported in middle-aged men (8), a distribution that likely reflects the burden of atherosclerotic risk factors in that population, including hypertension, dyslipidemia, diabetes, and smoking (22).

Medications constitute the most common trigger for Kounis syndrome (23). In a 2019 series, 142 of 252 cases (56.3%) were drug-induced (24). In the present case, which involves a young woman with a low atherosclerotic risk profile, onset plausibly relates to exposure to drugs or other agents known to precipitate anaphylaxis and mast-cell degranulation (11). We document a type I Kounis presentation without chest pain in a young female patient. Because Kounis syndrome is typically described in men aged 40–70 years and commonly accompanied by chest pain (8), a painless presentation in a young woman is uncommon. Clinicians evaluating patients with severe allergic reactions, including anaphylaxis, should consider concurrent acute coronary syndrome irrespective of age, sex, or the presence of chest pain.

Among patients with allergic reactions, in-hospital mortality has been reported at 7.0% for those with concomitant acute coronary syndrome attributed to Kounis syndrome, compared with 0.4% in those without acute coronary involvement (6). Higher rates of stroke and venous thrombosis have also been observed in this population (6). These outcomes underscore the need for rapid recognition and timely management. In most cases, symptom onset occurs within one hour of exposure to the inciting trigger (8). When Kounis syndrome is suspected, prompt 12-lead electrocardiography and transthoracic echocardiography are recommended, with early consideration of vasodilator therapy or coronary angiography when clinically indicated.

In this case, the induced vasospasm led to an increase in cardiac injury biomarkers, which gradually decreased over time toward reference values, indicating ischemia. Prolonged vasospasm caused myocardial cell necrosis, resulting in an increase in the cardiac-specific biomarker troponin. The spasm persisted at a high level for hours and then gradually returned to reference values over the course of days.

Kounis syndrome is a less heavily studied topic compared to other cardiovascular diseases. Therefore, existing protocols have not adequately addressed this condition. In a cross-sectional study published in March 2025 (25) on 150 cases of Kounis syndrome, coronary angiography was performed in only 119 cases. This leaves space for the cardiologist to assess the necessity of coronary angiography or other diagnostic approaches on a case-by-case basis.

Management of Kounis syndrome differs from that of other acute coronary syndromes because it requires concurrent treatment of the underlying allergic reaction. Intravenous corticosteroids and H1 and H2 antihistamines are commonly used as part of the initial approach. For types II and III, standard reperfusion strategies are required in addition to antiallergic therapy (4). Early diagnosis and coordinated treatment targeting both coronary and allergic pathophysiology are essential to improve outcomes.

CONCLUSION

Kounis syndrome, although uncommon in young women and particularly rare without chest pain, should remain in the differential diagnosis for any severe systemic allergic reaction, including anaphylaxis. Clinical management should be protocol driven: after initial stabilization, obtain a 12-lead ECG, perform serial high-sensitivity troponin testing, conduct bedside transthoracic echocardiography, and involve cardiology early, with coronary angiography considered when clinically indicated. Treatment must address both the allergic cascade and myocardial ischemia, with careful selection of agents that do not exacerbate coronary vasospasm.

This case underscores two practice-critical points. First, absence of chest pain does not exclude acute coronary involvement in anaphylaxis; ECG changes and elevations in hs-troponin require immediate interpretation and action. Second, the differential diagnosis should explicitly consider epinephrine-induced vasospasm, Takotsubo cardiomyopathy, and myocarditis, because therapeutic decisions depend on their distinction.

Given the documented risk of adverse outcomes and the persistent under-recognition of this entity, institutions should implement standardized operating procedures in emergency and critical care settings, provide targeted staff education, and integrate allergy and cardiology input early in the care pathway. Timely diagnosis coupled with coordinated therapy is essential to reduce morbidity and mortality in Kounis syndrome.

Finding: This research received no external funding or sponsorship.

Conflict of Interest Statement: The authors declare that there is no conflict of interest related to this paper.

Author Contribution & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. All authors contributed equally to the writing of this paper.

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

Sažetak

NEOBIČNA PREZENTACIJA KOUNISOVOG SINDROMA TIPA I: VISOK TROPONIN BEZ BOLA U GRUDIMA NAKON ANAFILAKSE

Čekić Said,[1, 2] Gutić Medo,[3] Milidrag Ardea[4]

[1] Zavod za hitnu medicinsku pomoć Crne Gore, Plav, Crna Gora
[2] Univerzitet u Travniku, Farmaceutsko-zdravstveni fakultet, Travnik, Bosna i Hercegovina
[3] JZU Dom zdravlja „Dr Branko Zogović“, Plav, Crna Gora
[4] Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Kragujevac, Srbija

Uvod: Kounisov sindrom se definiše kao istovremenost akutnog koronarnog sindroma i alergijskih ili anafilaktičkih reakcija. Prvenstveno pogađa muškarce u dobi od 40 do 70 godina i često je povezan s bolovima u grudima. Ovaj sindrom često ostaje neprepoznat i nedijagnostikovan u kliničkoj praksi zbog niskog nivoa informisanosti.

Prikaz slučaja: Ovde predstavljamo slučaj Kounisovog sindroma tipa I kod mlade žene bez bolova u grudima. Radi se o mladoj ženi sa dijagnozom alergijske astme od detinjstva, kod koje se tokom aplikacije bronhodilatatora, kortikosteroida i antibiotika u ambulanti HMP, desio anafilaktički šok, zastoj rada srca i kasnije po laboratorijskim nalazima dokazan akutni koronarni sindrom.

Zaključak: Iako je Kounisov sindrom dosta redak, naročito kod mladih žena, ipak treba usmeriti pažnju kod alergijskih rekacija teže kliničke prezentacije, na mogučnost razvoja akutnog koronarnog sindroma. Ovde smo kroz snimak EKG i kasnije laboratorijskim testovima potvrdili oštećenje na srčanom mišiću preko markera koronoranog sindroma.

Ključne reči: alergijska reakcija, akutni koronarni sindrom, reanimacija.

REFERENCES

1. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin Chem Lab Med. 2016; 54(10): 1545-59. doi: 10.1515/cclm-2016-0010.

2. Kounis NG. Coronary hypersensitivity disorder: the Kounis syndrome. Clin Ther. 2013; 35(5): 563–71. doi: 10.1016/j.clinthera.2013.02.022.

3. Biteker M, Biteker FS, Özlek B, Özlek E, Başaran N. Classification of Kounis syndrome. Int J Cardiol. 2017; 247:13. doi: 10.1016/j.ijcard.2017.06.002.

4. Kounis NG, Koniari I, Velissaris D, Tzanis G, Hahalis G. Kounis syndrome-not a single-organ arterial disorder but a multisystem and multidisciplinary disease. Balkan Med J. 2019; 36: 212–21. doi: 10.4274/balkanmedj.galenos.2019.2019.5.62.

5. Akoz A, Tanboga HI, Emet M, Bayramoglu A, Kizrak Y, Kantarci M, et al. A prospective study of Kounis syndrome: clinical experience and cardiac magnetic resonance imaging findings for 21 patients. Acta Med Mediterr. 2013; 29(4): 811–6.

6. Desai R, Parekh T, Patel U, Fong HK, Samani S, Patel C, et al. Epidemiologyof acute coronary syndrome co-existent with allergic/hypersensitivity/anaphylactic reactions (Kounis syndrome) in the United States: a nationwide inpatient analysis. Int J Cardiol. 2019;292:35–8. doi: 10.1016/j.ijcard.2019.06.002.

7. Kounis NG, Cervellin G, Koniari I, Bonfanti L, Dousdampanis P, Charokopos N,et al. Anaphylactic cardiovascular collapse and Kounis syndrome: systemic vasodilation or coronary vasoconstriction? Ann Transl Med. 2018; 6(17): 332. doi: 10.21037/atm.2018.09.05.

8. Abdelghany M, Subedi R, Shah S, Kozman H. Kounis syndrome: a review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome. Int J Cardiol. 2017; 232:1–4. doi: 10.1016/j.ijcard.2017.01.124.

9. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005; 352(5): 539–48. doi: 10.1056/NEJMoa043046.

10. Soufras GD, Kounis NG. Adrenaline administration for anaphylaxis and the risk of takotsubo and Kounis syndrome. Int J Cardiol. 2013; 166(2): 281–2 doi: 10.1016/j.ijcard.2012.12.075.

11. Kounis NG, Koniari I, Tsigkas G, Soufras GD, Plotas P, Davlouros P, et al. Angina following anaphylaxis: Kounis syn-

drome or adrenaline effect? Malays Fam Physician. 2020; 15(3): 97–8.

12. Rubio Caballero JA, Oteo Domínguez JF, Maicas Bellido C, Cantón T, BarcielaR, García Moreno LM et al. Vasoespasmo inducido por adrenalina como formade presentación de una angina variante [An adrenaline-induced vasospasmas the form of presentation of variant angina]. Rev Esp Cardiol. 1999; 52(4): 273-6. [Article in Spanish]. doi: 10.1016/S0300-8932(99)74911-0.

13. Saff R, Nahhas A, Fink JN. Myocardial infarction induced by coronary vasospasm after self-administration of epinephrine. Ann Allergy. 1993; 70(5): 396–8.

14. Shaver KJ, Adams C, Weiss SJ. Acute myocardial infarction after administrationof low-dose intravenous epinephrine for anaphylaxis. CJEM. 2006; 8(4): 289–94. doi: 10.1017/s1481803500013890

15. Kawakami T, Ando T, Kimura M, Wilson BS, Kawakami Y. Mast cells in atopicdermatitis. Curr Opin Immunol. 2009; 21(6): 666–78. doi: 10.1016/j.coi.2009.09.006

16. Liu FT, Goodarzi H, Chen HY. IgE, mast cells, and eosinophils in atopic dermatitis. Clin Rev Allergy Immunol. 2011; 41(3): 298–310. doi: 10.1007/s12016-011-8252-4.

17. Sederholm Lawesson S, Isaksson RM, Thylén I, Ericsson M, Ängerud K, Swahn E, et al. Gender differences in symptom presentation of ST-elevation myocardial infarction – an observational multicenter survey study. Int J Cardiol. 2018; 264: 7–11. doi: 10.1016/j.ijcard.2018.03.084.

18. Mehta PK, Wei J, Shufelt C, Quesada O, Shaw L, Bairey Merz CN. Gender related differences in chest pain syndromes in the frontiers in CV medicine special issue: sex & gender in CV medicine. Front Cardiovasc Med. 2021; 8: 744788. doi: 10.3389/fcvm.2021.744788.

19. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth. 2013; 111(1): 52–8. doi: 10.1093/bja/aet127.

20. Craft RM. Modulation of pain by estrogens. Pain. 2007;132(Suppl 1): S3–S12. doi: 10.1016/j.pain.2007.09.028.

21. Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppe RA, Zubieta JK. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. J Neurosci. 2006; 26(21): 5777–85. doi: 10.1523/JNEUROSCI.5223-05.2006.

22. Giovannini M, Koniari I, Mori F, Ricci S, De Simone L, Favilli S, et al. Kounis syndrome: a clinical entity penetrating from pediatrics to geriatrics. J Geriatr Cardiol. 2020; 17(5):294–9. doi: 10.11909/j.issn.1671-5411.2020.05.011.

23. Ollo-Morales P, Gutierrez-Niso M, De-la-Viuda-Camino E, Ruiz-de-GalarretaBeristain M, Osaba-Ruiz-de-Alegria I, Martel-Martin C. Drug-induced Kounis syndrome: latest novelties. Curr Treat Options Allergy. 2023: 1–18. doi: 10.1007/s40521-023-00342-9.

24. Raschi E, Fertonani Affini L, Antonazzo IC, Diemberger I, Poluzzi E, De Ponti F. Drug-induced Kounis syndrome: a matter of pharmacovigilance. Int J Cardiol. 2019; 274: 381. doi: 10.1016/j.ijcard.2018.07.119.

25. Rochel-Perez E, Santaularia-Tomas M, Martin-Dorantes M, Villareal-Jimenez E, Olivera-Mar A, Sanchez-Felix E, et al. Triggers, types, and treatments for Kounis syndrome: a systematic review. Clin Pract. 2025; 15(3): 59. doi: 10.3390/clinpract15030059.

Correspondence to/Autor za korespondenciju
Said Čekić,
Sarajevska 7, 84326 Gusinje, Montenegro
phone: +382 68 818 555
email: cekicsaid@gmail.com

How to cite this article*:* Čekić S**,** Gutić M, Milidrag A. An unusual presentation of Type I Kounis syndrome high troponin without chest pain after anaphylaxis. Sanamed. 2025; 20(3): 275-279. doi: 10.5937/sanamed20-62340.

SANAMED
2025; 20(3): 281–286
ISSN-1452-662X

DOI: 10.5937/sanamed0-60777
UDK: 616-022.1:617-089; 615.33
ID: 183773449
Review article

ANTIMICROBIAL STEWARDSHIP ACROSS THE SURGICAL PATHWAY

Sartelli Massimo,[1, 2] Detanac Dzemail[3]

[1] Department of Surgery, Macerata Hospital, Macerata, Italy
[2] Global Alliance for Infections in Surgery
[3] General Hospital Novi Pazar, Department of Surgery, Novi Pazar, Serbia

Primljen/Received: 11. 08. 2025. Prihvaćen/Accepted: 04. 10. 2025. Online First: 31. 10. 2025.

Abstract: Antimicrobial stewardship programs (ASPs) help ensure antibiotics are used effectively to treat infections, reduce side effects, and slow the spread of antibiotic resistance. Improving collaboration among healthcare professionals is the most important way to strengthen ASPs in hospitals.

So far, most ASPs have focused on medical specialities and applied the same approach to all hospital settings. In surgery, it is essential to understand the local cultural and contextual factors that shape prescribing habits so targeted strategies can be developed. Antibiotic stewardship in surgery must be integrated with strict infection prevention and source control, as all three work together to improve patient care.

Effective ASPs usually combine persuasive strategies, which educate and influence prescribers, with restrictive ones, which limit certain practices. While clinical guidelines turn evidence into practice and improve the quality of care, they do not always fit local realities. Adapting them into locally relevant tools, such as protocols, bundles, checklists, and posters, can boost acceptance and adherence. Actively involving prescribers in developing these tools increases the likelihood of meaningful change. Clearly defining responsibilities for specific actions within these protocols helps ensure they are followed.

Keywords: antimicrobial stewardship, antibiotic resistance, antibiotic prescribing, infection prevention, source control, multimodal approach.

INTRODUCTION

Antibiotics have played a crucial role in saving countless lives and making surgical procedures much safer. Safe surgical care relies heavily on access to effective antibiotics to prevent and treat infections. Yet, despite their vital role, antibiotics are frequently used inappropriately, creating challenges in surgical practice. Improving antibiotic prescribing in surgery is essential to enhance patient outcomes, reduce the risk of side effects, and curb the spread of antimicrobial resistance (AMR).

The multimodal approach to infections

Strategies to optimise antibiotic use in surgery involve a multimodal approach, primarily based on infection prevention and control measures, which are essential to reduce the use of broad-spectrum antibiotics in hospitals. Infection prevention and control (IPC) programmes are an integral part of modern healthcare systems, using evidence-based approaches to prevent healthcare-associated infections (HAIs). Patients with HAIs often require additional diagnostic and therapeutic interventions, have prolonged hospital stays, incur extra costs, and face higher morbidity and mortality risks. In particular, managing patients with HAIs often requires broad-spectrum antibiotic regimens due to the high risk of multidrug-resistant bacteria (1).

Surgical patients are especially susceptible to hospital-acquired infections and more vulnerable to their consequences. Surgical site infections (SSIs) are the leading type of hospital-acquired infection in surgical patients. Recently, many sets of guidelines based on evidence have been developed for preventing SSIs throughout all stages of surgery—before, during, and after the procedure (2–8). Despite this, compliance with these recommended best practices remains low (9). Furthermore, other healthcare-associated infections—such as catheter-associated urinary tract infections, central-line–associated bloodstream infections, hospital-acquired pneumonia, ventilator-associated pneumonia, and Clostridioides difficile infections—represent major safety concerns in postoperative care.

Since many hospital-acquired infections are partly preventable, implementing prevention strategies is

essential for patient safety in hospitals (10). Nevertheless, healthcare workers often fail to adhere to evidence-based preventive measures (11). A prime example is hand hygiene, considered both a patient safety indicator and the cornerstone of IPC in all healthcare settings. Although universally recognised as effective and cost-efficient, hand hygiene compliance remains unacceptably low.

In surgery, antibiotics play a major role, prescribed either as surgical prophylaxis or therapy. Surgical antibiotic prophylaxis (SAP) significantly contributes to overall antibiotic use in hospitals, accounting for around 15% of all prescriptions (12). SAP is recommended for clean-contaminated procedures with an increased SSI risk or clean procedures where even unlikely SSIs could have severe consequences—such as those involving prosthetic implants. However, antibiotics alone cannot prevent SSIs, and all prevention measures must be implemented alongside them (13).

In general, SAP should be administered 30–60 minutes before incision for the most commonly used antibiotics (including cefazolin). Intraoperative re-dosing is indicated for surgeries exceeding twice the antibiotic's half-life or involving significant blood loss. In principle, SAP should always be discontinued after surgery. Unfortunately, inappropriate SAP prescribing remains consistently high in surgical settings (14).

Antibiotic therapy is a cornerstone of daily surgical practice, with surgeons often on the frontline of managing patients with complicated infections. Because microbiology results take time, antibiotic therapy is initially empirical, prescribed based on symptoms and likely pathogens. Targeted therapy begins once microbial identification and susceptibility results are available, ensuring effective antibiotic use. Optimal targeted therapy requires early pathogen identification, but even with advances in rapid diagnostics, microbiology results can take up to 72 hours.

Surgeons should acknowledge that proper antibiotic prescribing is a core part of surgical practice and recognise that antibiotic stewardship is closely linked to surgical work, playing a key role in both patient care and treatment effectiveness (15).

A recent call to action highlighted the importance of optimal antibiotic use in hospitals, proposing ten "golden rules" to guide clinicians—emphasising the need to prescribe the right antibiotic for the right patient, at the right dose, via the right route, for the right duration—and stressing a collaborative approach to uphold these principles (2).

In surgical infections, source control is both feasible and highly impactful for improving patient outcomes. Appropriate source control can enhance recovery and reduce antibiotic use, allowing for shorter treatment courses. Source control encompasses measures to eliminate the infection source and stop ongoing contamination, requiring a thorough understanding of pathophysiology, host response, surgical and nonsurgical options, and a balanced mix of therapeutic aggressiveness and cautious decision-making.

The reduction of antibiotic treatment duration for patients with complicated intra-abdominal infections is now well established, especially when optimal source control is achieved. In such cases, short antibiotic courses following adequate source control are a reasonable option (16).

Antimicrobial stewardship programs (ASP) in surgery

Antimicrobial stewardship programs (ASPs) are now considered a key initiative to optimise antibiotic use, improve patient outcomes, and curb AMR emergence. ASPs can optimise antibiotic therapy and reduce antibiotic-associated adverse events (17). Evidence shows they can significantly reduce multidrug-resistant bacterial infections and *C. difficile* colonisation in hospitals. Hospitals worldwide should leverage existing resources to organise effective interdisciplinary teams (18, 19).

Fifteen years after the first joint guidelines for institutional ASP development (20), practices remain poorly defined and vary according to local models and available resources. Traditionally, hospital ASPs have focused mainly on medical specialities, often applying a one-size-fits-all approach across settings. However, antibiotic decision-making for surgical patients should be developed separately and requires a necessarily collaborative approach involving a multidisciplinary network.

Key ASP strategies should combine persuasive and restrictive approaches. Persuasive strategies aim to improve prescriber knowledge, shift attitudes, and influence prescribing behaviour through persuasion—generally better accepted and more educational than restrictive strategies, which, while potentially more effective short term, do not actively engage surgeons in changing behaviour.

Preauthorisation means that prescribers must obtain permission before they can prescribe specific antibiotics. This can reduce unnecessary or inappropriate antibiotic use, particularly for preserving newer-generation drugs for multidrug-resistant infections. In some contexts, preauthorisation also applies to drugs such as fluoroquinolones, now recommended only in specific cases due to side effects and resistance potential. Evidence supports restrictive interventions when urgent, but shows persuasive and restrictive strategies to be equally effective long term. However, preauthorisation can be time-consuming, and some hospitals lack staff to manage it.

Restrictive measures overlook the appropriateness of unrestricted antibiotics, which make up the majority of hospital prescriptions, potentially leading to increased use of these drugs—a phenomenon known as the "squeezing the balloon" effect. Additionally, restricting antibiotics may impact surgeon autonomy, creating barriers to collaboration and reducing essential communication for effective stewardship.

Improving hospital ASPs should always involve interprofessional collaboration. ASPs should include infectious disease specialists and clinical pharmacists trained in infectious diseases, closely allied with clinical microbiologists. Infection prevention specialists and hospital epidemiologists should coordinate infection monitoring and prevention, with strong support from hospital administrators. Importantly, surgeons' involvement in ASPs is essential.

Studies have shown low surgeon awareness regarding antibiotic prescribing, with antibiotics often considered a low-priority task (21). Surgeons tend to prioritise surgical outcomes, with fear of poor results outweighing concerns over inappropriate prescribing. This can lead to extended prophylaxis, delayed discontinuation post-surgery, or prolonged therapy after source control. Limited ward time due to operating theatre demands often shifts responsibility to junior staff without decision-making authority. Thus, expecting surgeons to fully integrate stewardship into daily practice can be challenging (22).

To improve prescribing initiatives, structural and cultural determinants of antibiotic use in surgery must be addressed. Factors such as fear of clinical failure, time pressure, and organisational constraints complicate decision-making. Due to cognitive dissonance—knowing an action is needed but failing to take it—changing prescribing behaviour is difficult.

Raising surgeon awareness about appropriate antibiotic use is therefore essential. Individually, each physician should have the knowledge, skills, and abilities to implement effective prescribing practices. Antibiotic prescribing education should be part of all medical training, including surgical curricula. While increasing knowledge can influence perceptions and motivate change, knowledge alone is rarely enough for lasting improvement, as habits and established practices are hard to alter.

Training alone has a limited impact without accompanying interventions. Successful strategies have included adapting guidelines into local protocols, defining specific responsibilities, and actively involving surgeons. Such engagement can lead to meaningful cultural change towards shared protocol adherence. Conversely, restrictive, punitive mandates should be avoided, as they tend to foster only superficial compliance.

Hospitals with strong safety cultures can promote education, communication, and collaboration. In this environment, surgeons are more likely to engage with infectious disease specialists, hospital pharmacists, and microbiologists.

A prospective audit and feedback strategy is a common stewardship intervention, aiming to maintain prescriber autonomy while improving antibiotic use (23). This strategy is particularly suitable for surgery, is better accepted than restrictive approaches, and provides educational opportunities through feedback. In surgery, it has been associated with shorter hospital stays and treatment durations (24, 25).

Identifying a local opinion leader or "champion" is also important, as such individuals can integrate best practices, motivate peers, and collaborate with IPC and ASP teams. This "champion" model has already proven effective in surgical safety initiatives such as checklists.

Future directions

To further strengthen antimicrobial stewardship in surgery, innovative strategies should be explored. Digital prescribing tools, such as electronic prescribing systems with built-in clinical decision support, can help guide antibiotic choice, timing, and duration, while also flagging inappropriate practices in real time. Similarly, rapid diagnostic technologies offer opportunities for earlier pathogen identification and antimicrobial susceptibility testing, reducing unnecessary empirical therapy and allowing faster transitions to targeted treatment.

Another promising area involves the application of structured behavioural science methods to address cultural and psychological drivers of antibiotic prescribing. Approaches such as nudges, feedback loops, and behavioral incentives can complement traditional educational and guideline-based interventions, making stewardship efforts more sustainable.

At the same time, stewardship strategies must be realistic and adaptable to low-resource settings, where access to diagnostics, trained personnel, and digital infrastructure may be limited. In such environments, simplified protocols, context-specific guidelines, and innovative capacity-building models are essential. Implementation science approaches should be used to anticipate barriers and design scalable solutions that maintain effectiveness while fitting local realities (26).

CONCLUSION

ASPs can optimize antibiotic treatment and reduce adverse events. To date, hospital ASPs have largely focused on medical specialities with uniform approaches, but understanding the contextual and cul-

tural factors behind surgical prescribing is essential for targeted interventions. Antimicrobial stewardship cannot be separated from infection prevention/control and appropriate source control, as all three are interconnected throughout the surgical pathway.

The best way to improve stewardship in general and emergency surgical units worldwide is to foster cross-speciality collaboration. Identifying a local "champion" can help integrate best practices and drive behavioural change. Surgeons with expertise in surgical infections, when involved in ASPs, can review prescriptions, provide feedback, promote best practices, and serve as liaisons between IPC and stewardship teams.

Key ASP strategies should combine persuasive and selective restrictive measures. While guidelines can translate evidence-based practices into clinical reality, they must be adapted locally to improve acceptance and adherence. Local protocols, bundles, checklists, and posters can help, especially when prescribers are directly involved in their development.

A prospective audit and feedback strategy, by preserving prescriber autonomy while enhancing prescribing quality, is easily applicable to surgery. Ultimately, collaboration is essential for maximising patient outcomes and improving healthcare delivery. Multidisciplinary teams bring together specialised skills to deliver coordinated care through agreed-upon plans.

Abbreviations

ASP - Antimicrobial Stewardship Program
AMR - Antimicrobial Resistance
IPC - Infection Prevention and Control
HAI(s) - Healthcare-Associated Infection(s)
SSI(s) - Surgical Site Infection(s)
SAP - Surgical Antibiotic Prophylaxis
C. difficile - *Clostridioides difficile*
OR - Operating Room

Conflict of Interest Statement

The authors declare that there is no conflict of interest related to this paper.

Funding: None

Author Contributions & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. All authors contributed equally to the preparation of this manuscript.

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

Sažetak

NADZOR I KONTROLA KORIŠĆENJA ANTIMIKROBNIH LEKOVA U HIRURGIJI

Sartelli Massimo,[1, 2] Detanac Dzemail[3]

[1] Odeljenje hirurgije Macerata bolnice, Macerata, Italija
[2] Globalna alijansa za infekcije u hirurgiji
[3] Opšta bolnica Novi Pazar, Odeljenje opšte hirurgije, Novi Pazar, Srbija

Programi za racionalnu upotrebu antibiotika (eng. Antimicrobial Stewardship Programs – ASP) pomažu u osiguravanju efikasne primene antibiotika za lečenje infekcija, smanjenju neželjenih efekata i usporavanju širenja rezistencije na antibiotike. Poboljšanje saradnje među zdravstvenim profesionalcima predstavlja ključni način za jačanje ovih programa u bolnicama.

Do sada se većina ovih programa fokusirala na medicinske specijalnosti i primenjivala isti pristup u svim bolničkim sredinama. U hirurgiji je od suštinskog značaja razumevanje lokalnih kulturnih i kontekstualnih faktora koji oblikuju navike propisivanja antibiotika, kako bi se razvile ciljne strategije. Racionalna upotreba antibiotika u hirurgiji treba da bude integrisana sa strogom prevencijom infekcija i kontrolom izvora infekcije, jer sve tri komponente deluju zajedno na poboljšanje nege pacijenata.

Efikasni ASP obično kombinuju uverljive strategije, koje edukuju i utiču na lekare koji propisuju lekove, sa restriktivnim strategijama, koje ograničavaju određene prakse. Iako kliničke smernice prevode dokaze u praksu i poboljšavaju kvalitet nege, one se ne uklapaju uvek u lokalne realnosti. Njihova adaptacija u lokalno relevantne alate, poput protokola, „bundlova", kontrolnih lista i postera, može povećati prihvatanje i pridržavanje. Aktivno uključivanje propisivača lekova u razvoj ovih alata povećava verovatnoću značajnih promena u praksi. Jasno definisanje odgovornosti za specifične aktivnosti unutar protokola pomaže da se osigura njihovo sprovođenje.

***Ključne reči**:* racionalna upotreba antibiotika, rezistencija na antibiotike, propisivanje antibiotika, prevencija infekcija, kontrola izvora infekcije, multimodalni pristup.

REFERENCES

1. Sartelli M, Labricciosa FM, Barbadoro P, Pagani L, Ansaloni L, Brink AJ, et al. The Global Alliance for Infections in Surgery: defining a model for antimicrobial stewardship—results from an international cross-sectional survey. World J Emerg Surg. 2017; 12:34. doi: 10.1186/s13017-017-0145-2.

2. Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. Ten golden rules for optimal antibiotic use in hospital settings: the WARNING call to action. World J Emerg Surg. 2023; 18(1): 50. doi: 10.1186/s13017-023-00518-3.

3. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016; 16(12): e288-e303. doi: 10.1016/S1473-3099(16)30402-9.

4. Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016; 16(12): e276-87. doi: 10.1016/S1473-3099(16)30398-X.

5. Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg. 2017; 152(8): 784-91. doi: 10.1001/jamasurg.2017.0904.

6. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. American College of Surgeons and Surgical Infection Society: surgical site infection guidelines, 2016 Update. J Am Coll Surg. 2017 Jan; 224(1): 59-74. doi: 10.1016/j.jamcollsurg.2016.10.029.

7. National Institute for Health and Care Excellence. Surgical site infections: prevention and treatment. NICE guideline [NG125]. Available at: https://www.nice.org.uk/guidance/ng125. Last accessed: 18 November 2024.

8. Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014; 35(6): 605-27. doi: 10.1086/676022.

9. Sartelli M, Bartoli S, Borghi F, Busani S, Carsetti A, Catena F, et al. Implementation strategies for preventing healthcare-associated infections across the surgical pathway: an Italian multisociety document. Antibiotics (Basel). 2023; 12(3): 521. doi: 10.3390/antibiotics12030521.

10. Schreiber PW, Sax H, Wolfensberger A, Clack L, Kuster SP; Swissnoso. The preventable proportion of healthcare-associated infections 2005-2016: Systematic review and meta-analysis. Infect Control HospEpidemiol. 2018; 39(11): 1277-95. doi: 10.1017/ice.2018.183.

11. Sartelli M, Labricciosa FM, Coccolini F, Coimbra R, Abu-Zidan FM, Ansaloni L, et al. It is time to define an organizational model for the prevention and management of infections along the surgical pathway: a worldwide cross-sectional survey. World J Emerg Surg. 2022; 17(1): 17. doi: 10.1186/s13017-022-00420-4.

12. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013; 70(3): 195-283. doi: 10.2146/ajhp120568.

13. Sartelli M, Coccolini F, Labricciosa FM, Al Omari AH, Bains L, Baraket O, et al. Surgical antibiotic prophylaxis: a proposal for a global evidence-based bundle. Antibiotics (Basel). 2024; 13(1): 100. doi: 10.3390/antibiotics13010100.

14. Ierano C, Thursky K, Marshall C, Koning S, James R, Johnson S, et al. Appropriateness of surgical antimicrobial prophylaxis practices in Australia. JAMA Netw Open. 2019; 2(11): e1915003. doi: 10.1001/jamanetworkopen.2019.15003.

15. Sartelli M, Duane TM, Catena F, Tessier JM, Coccolini F, Kao LS, et al. Antimicrobial stewardship: a call to action for surgeons. Surg Infect (Larchmt). 2016; 17(6): 625-31. doi: 10.1089/sur.2016.187.

16. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015; 372(21): 1996-2005. doi: 10.1056/NEJMoa1411162.

17. Global Alliance for Infections in Surgery collaborators group. A global declaration on appropriate use of antimicrobial agents across the surgical pathway. Surg Infect (Larchmt). 2017; 18(8): 846-53. doi: 10.1089/sur.2017.219.

18. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013; (4): CD003543. doi: 10.1002/14651858.CD003543.pub3.

19. Goff DA, Kullar R, Goldstein EJC, Gilchrist M, Nathwani D, Cheng AC, et al. A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. Lancet Infect Dis. 2017; 17(2): e56-e63. doi: 10.1016/S1473-3099(16)30386-3.

20. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007; 44(2): 159-77. doi: 10.1086/510393.

21. Charani E, Tarrant C, Moorthy K, Sevdalis N, Brennan L, Holmes AH. Understanding antibiotic decision making in surgery-a qualitative analysis. Clin Microbiol Infect. 2017; 23(10): 752-60. doi: 10.1016/j.cmi.2017.03.013.

22. Charani E, Ahmad R, Rawson TM, Castro-Sanchèz E, Tarrant C, Holmes AH. The differences in antibiotic decision-making between acute surgical and acute medical teams: an ethnographic study of culture and team dynamics. Clin Infect Dis. 2019; 69(1): 12-20. doi: 10.1093/cid/ciy844.

23. Brink AJ, Messina AP, Feldman C, Richards GA, van den Bergh D; Netcare Antimicrobial Stewardship Study Alliance. From guidelines to practice: a pharmacist-driven prospective audit and feedback improvement model for peri-operative antibiotic prophylaxis in 34 South African hospitals. J Antimicrob Chemother. 2017; 72(4): 1227-34. doi: 10.1093/jac/dkw523.

24. Elligsen M, Walker SA, Simor A, Daneman N. Prospective audit and feedback of antimicrobial stewardship in critical care: program implementation, experience, and challenges. Can J Hosp Pharm. 2012; 65(1): 31-6. doi: 10.4212/cjhp.v65i1.1101.

25. Chan AJ, Tsang ME, Langford BJ, Nisenbaum R, Wan M, Downing MA. Evaluating a pilot, structured, face-to-face,

antimicrobial stewardship, prospective audit-and-feedback program in emergency general surgery service in a community hospital. Antimicrob Steward HealthcEpidemiol. 2023; 3(1): e96. doi: 10.1017/ash.2023.168.

26. Sartelli M. Leveraging the synergy between antimicrobial stewardship and infection prevention and control in fighting antimicrobial resistance. Sanamed. 2021; 16(3): 231-3. doi: 10.24125/sanamed.v16i3.524.

Correspondence to/Autor za korespondenciju
Massimo Sartelli
Department of Surgery, Macerata Hospital, Macerata, Italy
https://orcid.org/0000-0003-3202-7542
email: massimosartelli@gmail.com

Detanac Dzemail Orcid No 0000-0002-4823-5867

***How to cite this article**:* Sartelli M, Detanac Dz. Antimicrobial stewardship across the surgical pathway. Sanamed. 2025; 20(3): 281-286. doi: 10.5937/sanamed0-60777.

SANAMED
2025; 20(3): 287–293
ISSN-1452-662X

DOI: 10.5937/sanamed20-62422
UDK: 616-089.16
ID: 183862793
Review article

BRIDGING PRIMARY CARE AND SURGERY: THE ROLE OF GENERAL PHYSICIANS AND ANESTHESIOLOGISTS IN PERIOPERATIVE OPTIMIZATION

Domi Rudin, Kaci Myzafer

University of Medicine, Faculty of Medicine, Department of Surgery, Tirana, Albania

Primljen/Received: 27. 10. 2025. Prihvaćen/Accepted: 20. 12. 2025.

Abstract: The transition of a patient from primary or internal medicine care to the operating room represents a critical juncture in perioperative management. Surgical patients requiring anesthesia must undergo thorough, multidisciplinary preparation involving family physicians, internists, hospitalists, anesthesiologists, surgeons, and physiotherapists. This multidimensional approach helps ensure a safe and seamless transition to anesthesia and surgery, thereby optimizing procedural outcomes. Key challenges during this phase include accurate assessment of physical status, risk stratification, optimization of comorbidities, and management of chronic medications. Adequate preoperative preparation minimizes the risk of surgical delays and enhances patient safety. This paper aims to highlight critical issues that can be addressed collaboratively by general physicians and anesthesiologists, fostering improved communication, shared knowledge, and clinical expertise.

Key words: perioperative medicine, anesthesia, surgery, chronic medications, comorbidities, perioperative risk stratification.

INTRODUCTION

The transition of patients from primary care or internal medicine services to the operating room represents a pivotal and complex stage in perioperative management. This phase is not merely a logistical handover; it is a critical period during which careful assessment, optimization, and planning directly influence patient safety and surgical outcomes. Patients scheduled for surgery and requiring anesthesia must undergo comprehensive, multidisciplinary preparation. This involves collaboration among family physicians, internists, hospitalists, anesthesiologists, surgeons, and physiotherapists, each contributing unique expertise to ensure that the patient is optimally prepared for the operative procedure. Such a coordinated, team-based approach facilitates a smooth and safe transition to anesthesia and surgery, ultimately reducing perioperative risks and improving clinical outcomes.

Several key challenges arise during this transition. Accurate assessment of the patient's physical status is essential to identify potential perioperative risks. Risk stratification allows clinicians to anticipate complications and tailor interventions accordingly. Optimization of comorbidities, including cardiovascular, respiratory, metabolic, and renal conditions, is critical, as poorly controlled diseases can increase the likelihood of intraoperative and postoperative complications. Additionally, careful management of chronic medications, including anticoagulants, antiplatelets, antihypertensives, and other long-term therapies, is necessary to prevent adverse interactions and minimize surgical delays (1).

In real-world practice, several pitfalls commonly occur during preoperative preparation. For example, undiagnosed or poorly controlled hypertension can increase the risk of intraoperative hemodynamic instability, while unrecognized anemia may lead to unnecessary transfusions or delayed surgery. Inadequate patient counseling about perioperative fasting, medication adjustments, or postoperative expectations often results in confusion, anxiety, and last-minute cancellations. Furthermore, communication gaps between primary physicians and anesthesiologists can result in incomplete medical histories or missed risk factors (2).

Practical interventions to address these issues include structured preoperative assessment clinics, standardized checklists, and multidisciplinary team meetings. Family physicians and internists play a crucial role in optimizing chronic conditions before sur-

gery, while anesthesiologists focus on risk stratification and perioperative planning (3). Clear protocols for medication management, including bridging strategies for anticoagulation and antihypertensive adjustments, can prevent complications. Patient education initiatives, including preoperative counseling and written instructions, improve compliance and reduce anxiety. Adequate preoperative preparation not only enhances patient safety and minimizes perioperative complications but also improves operational efficiency by reducing the likelihood of last-minute cancellations or postponements due to incomplete or inadequate evaluation. Furthermore, this phase represents an opportunity for knowledge sharing and skills development between general physicians and anesthesiologists, strengthening interdisciplinary collaboration. This review aims to highlight essential aspects of preoperative care that can be effectively addressed through joint efforts of general physicians and anesthesiologists. By fostering greater collaboration, communication, and expertise, healthcare teams can optimize perioperative management, ensuring safer surgical journeys and better overall patient outcomes.

Perioperative optimization and postoperative mortality and morbidity

Preoperative optimization demonstrates the strongest mortality benefit in high-risk surgical patients, particularly through hemodynamic optimization and correction of anemia or malnutrition. Prehabilitation improves recovery and complication rates, although most trials are underpowered for mortality endpoints. Smoking cessation and restrictive transfusion thresholds are also associated with improved overall outcomes. A multidisciplinary, patient-tailored approach remains essential for achieving maximal benefit.

Preoperative optimization aims to identify and modify risk factors before surgery in order to reduce postoperative complications and mortality. Among the most studied interventions, goal-directed hemodynamic therapy (GDHT) has shown the most consistent mortality benefit. In pooled analyses of randomized controlled trials, GDHT significantly reduced short-term mortality (risk ratio 0.75; 95% CI 0.61–0.91), particularly in high-risk abdominal surgical populations (4).

In contrast, prehabilitation programs—including exercise training, inspiratory muscle exercises, nutritional support, and smoking cessation—demonstrate clear improvements in postoperative recovery but have not consistently reduced 30-day mortality. Although large systematic reviews confirm reductions in complications and hospital length of stay (LOS) by approximately one to two days, most trials remain underpowered for mortality outcomes (5).

Nutritional optimization, particularly through preoperative oral nutritional supplementation, has been associated with lower all-cause postoperative mortality in malnourished or frail patients, such as those undergoing gastrointestinal cancer or hip fracture surgery (6, 7). These interventions also reduce infections and improve nutritional biomarkers, supporting their role in high-risk populations.

Anemia remains an independent risk factor for postoperative death. Meta-analyses report approximately a 2.8-fold increase in the odds of mortality in anemic patients undergoing major or orthopedic surgery. Consensus guidelines therefore recommend identification and correction of anemia—using iron supplementation or erythropoietin when indicated—to reduce perioperative transfusion requirements and improve outcomes (8, 9).

Smoking cessation has an indirect yet clinically meaningful impact on postoperative survival through a reduction in severe complications. Studies demonstrate significant decreases in pulmonary and wound complications when cessation occurs at least two to four weeks preoperatively, particularly when combined with behavioral and pharmacologic support (10).

Finally, restrictive transfusion strategies during the perioperative period have been shown to be safe and non-inferior to liberal transfusion approaches with regard to short-term mortality. Restrictive thresholds reduce transfusion exposure without increasing death rates, although findings vary in specific subgroups, such as cardiac surgery and massive hemorrhage (11).

Overall, current evidence indicates that preoperative optimization enhances surgical safety, with the most pronounced mortality benefits observed in targeted, high-risk interventions—particularly hemodynamic optimization, correction of anemia, and nutritional support. Broader prehabilitation and behavioral interventions further improve recovery, reduce perioperative complications, and enhance physiological resilience, even when direct mortality reductions are not statistically significant. Moreover, collaboration between general or family physicians and perioperative specialists plays a pivotal role in preparing patients for elective surgery. This partnership facilitates early interventions such as smoking cessation, nutritional optimization, treatment of preoperative anemia, and structured rehabilitation, thereby ensuring a more comprehensive and effective preoperative preparation process. Table 1 summarizes quantitative evidence from systematic reviews and meta-analyses regarding the relationship between various preoperative optimization strategies and postoperative mortality.

Table 1. *Preoperative optimization and postoperative mortality: evidence summary*

Intervention (Target)	Effect on Mortality	Other Relevant Effects	Key Findings / Pooled Estimate	Reference (Vancouver)
Goal-directed hemodynamic therapy (GDHT)	Reduced short-term mortality (RR 0.75, 95% CI 0.61–0.91)	Reduced complications and LOS; benefit strongest in major/high-risk abdominal surgery.	Modern GDT protocols show mortality benefit.	Sun et al. (4)
Prehabilitation (exercise, nutrition, smoking cessation)	No consistent reduction in 30-day mortality; trials underpowered for this outcome.	Reduced complications, shorter LOS (~1–2 days), improved recovery.	Large systematic reviews/meta-analyses confirm benefits for complications and LOS.	Li N et al. (5)
Preoperative oral nutritional supplementation	Reduced all-cause postoperative mortality in malnourished or frail subgroups.	Reduced infections and complication rates; improved nutritional markers.	Effect clearer in malnourished or elderly surgical cohorts.	Knight et al., (6); Lai et al., (7).
Preoperative anemia correction	Anemia associated with increased mortality (OR ~2.78); treatment recommended.	Anemic patients need more transfusions; correction improves outcomes.	Consensus supports iron ± erythropoietin when indicated.	Fowler et al. (8); Buhl et al. (9)
Preoperative smoking cessation	No consistent mortality data; reduces severe postoperative complications.	Decreases pulmonary and wound complications when ≥4 weeks preop.	Combining behavioral and pharmacotherapy yields best results.	Mills et al. (10)
Restrictive vs liberal transfusion thresholds	No increase in short-term mortality; non-inferior to liberal strategy.	Reduces transfusion exposure; mixed findings in cardiac/massive hemorrhage.	Restrictive strategy safe across most surgical contexts.	Lenet et al. (11)

Consequences of postponing surgery

Inadequate preoperative preparation significantly contributes to adverse surgical outcomes. Poor optimization of comorbidities—such as anemia, malnutrition, diabetes, or cardiopulmonary disease—elevates the risk of intraoperative instability, postoperative complications, and mortality. Patients entering surgery in suboptimal condition are more susceptible to stress-induced decompensation, impaired wound healing, and infections. Additionally, uncontrolled metabolic status, inadequate nutrition, or untreated anemia can compromise oxygen delivery, tissue perfusion, and immune function (12).

Neglecting modifiable risk factors—including smoking, alcohol use, obesity, poor nutrition, or inappropriate medication management—further increases morbidity. These issues often arise from time constraints, fragmented communication, or insufficient pre-assessment pathways, leading to delayed recovery, prolonged hospitalization, higher readmission rates, and long-term morbidity. Beyond patient safety, these deficiencies undermine efficiency and quality within the surgical system (13).

Unplanned surgical delays pose additional risks. Postponements due to incomplete optimization or late detection of medical issues can worsen the underlying disease, deteriorate physiological status, and heighten patient anxiety. Even short delays may negatively impact prognosis in oncological, infectious, or cardiovascular conditions. Repeated cancellations also impose logistical burdens, wasting operating room time, increasing administrative workload, and disrupting hospital workflow—reflecting gaps in coordination, resource allocation, and interdisciplinary communication (14).

Structured preoperative assessment and timely optimization are therefore essential. Multidisciplinary preoperative clinics—including anesthesiologists, surgeons, internists, and family physicians—allow early identification and management of modifiable risk factors. Standardized protocols, early screening for anemia and malnutrition, and lifestyle interventions such as smoking cessation and physical conditioning improve postoperative outcomes, reduce cancellations, and enhance system efficiency (15).

Family physicians play a pivotal role in preoperative preparation, coordinating with surgeons, anesthesiologists, and perioperative teams to ensure patients achieve optimal medical and physical status before surgery. Multidisciplinary programs combining medical optimization, lifestyle guidance, and rehabilitation strengthen patient resilience and facilitate a safer and more efficient surgical pathway.

The internist's role in preoperative assessment and optimization

Preoperative evaluation by the internist is a critical determinant of perioperative outcomes in patients undergoing surgical procedures. Rather than serving as a simple clearance process, preoperative assessment aims to identify and optimize medical comorbidities, stratify perioperative risk, and facilitate coordinated, multidisciplinary perioperative care. Effective internist involvement has been associated with reduced perioperative morbidity and mortality, particularly in medically complex patients.

General principles of preoperative assessment

A comprehensive clinical assessment forms the foundation of preoperative evaluation. This includes a detailed medical history, assessment of functional capacity—commonly expressed in metabolic equivalents (METs)—a thorough review of current medications, and a focused physical examination. Current guidelines discourage routine preoperative testing in asymptomatic patients, emphasizing that laboratory and diagnostic investigations should be selectively ordered based on clinical findings, patient comorbidities, and the complexity and risk profile of the planned surgical procedure (16).

Cardiovascular risk stratification

Cardiovascular complications remain a leading cause of adverse perioperative events in non-cardiac surgery. Preoperative cardiac evaluation should integrate patient-specific clinical risk factors, validated risk prediction tools such as the Revised Cardiac Risk Index, the inherent risk of the surgical procedure, and the patient's functional capacity. Non-invasive cardiac testing should be reserved for selected patients in whom test results are likely to influence perioperative management or surgical decision-making. Optimization of heart failure, ischemic heart disease, hypertension, and cardiac arrhythmias is essential prior to elective surgery (17, 18).

Pulmonary risk assessment

Identification of patients at increased risk for postoperative pulmonary complications is a key component of preoperative preparation. Attention should be given to individuals with chronic obstructive pulmonary disease, asthma, obstructive sleep apnea, or a history of smoking. Evidence-based preventive strategies include preoperative smoking cessation, optimization of inhaled therapies, treatment of active respiratory infections, and implementation of lung expansion techniques to reduce postoperative pulmonary morbidity (19, 20).

Metabolic and endocrine considerations

Metabolic disorders, particularly diabetes mellitus, require structured perioperative planning. Poor preoperative glycemic control is associated with increased risks of surgical site infection, delayed wound healing, and adverse outcomes. The internist plays a central role in optimizing glycemic control and establishing individualized perioperative management plans for insulin and oral hypoglycemic agents, with the goal of avoiding both hypoglycemia and significant hyperglycemia (21).

Perioperative medication management

Medication management represents one of the most complex aspects of preoperative care. Decisions regarding the continuation or temporary discontinuation of anticoagulants, antiplatelet agents, antihypertensives, and chronic corticosteroid therapy must carefully balance bleeding risk, thromboembolic risk, and adrenal insufficiency. These decisions should be individualized and require close communication between the internist, anesthesiologist, and surgical team to ensure patient safety and continuity of care (22).

Frailty, nutrition, and anemia

There is growing recognition of frailty, malnutrition, and anemia as independent predictors of poor surgical outcomes. Preoperative identification of frailty allows for risk stratification and informed shared decision-making. Correction of anemia and nutritional optimization, particularly in elderly patients and those undergoing oncologic surgery, have been shown to improve postoperative recovery and reduce complication rates (23, 24).

Table 2. *Key components of preoperative assessment and optimization by the internist*

Domain	Key Elements	Internist's Role	Impact on Outcomes
Clinical evaluation	Medical history, functional capacity (METs), focused physical examination	Identify comorbidities, assess physiological reserve, guide need for further testing	Avoids unnecessary investigations; improves risk stratification (16)
Cardiovascular risk	RCRI, surgical risk, functional status	Optimize heart failure, ischemic heart disease, hypertension, arrhythmias; select patients for further testing	Reduces perioperative cardiac events (17, 18)
Pulmonary assessment	COPD, asthma, OSA, smoking status	Implement smoking cessation, optimize inhaled therapy, treat infections, plan lung expansion strategies	Lowers postoperative pulmonary complications (19, 20)
Metabolic/endocrine status	Diabetes mellitus, electrolyte disorders	Optimize glycemic control; plan perioperative insulin and oral agent management	Decreases infection risk and metabolic complications (21)
Medication management	Anticoagulants, antiplatelets, antihypertensives, steroids	Balance bleeding vs thrombotic risk; manage steroid stress dosing	Prevents hemorrhagic, thromboembolic, and adrenal complications (22)
Frailty and nutrition	Frailty scores, nutritional status	Identify vulnerable patients; initiate nutritional and functional optimization	Improves recovery and reduces postoperative morbidity (23, 24)
Anemia management	Hemoglobin levels, iron deficiency	Diagnose and treat anemia preoperatively	Reduces transfusion needs and adverse outcomes (23, 24)
Multidisciplinary coordination	Communication with surgery and anesthesia	Document risks, optimization strategies, and postoperative plans	Enhances continuity of care and patient safety

Multidisciplinary coordination and continuity of care

Effective perioperative management relies on structured multidisciplinary collaboration. Clear documentation of preoperative risk assessment, optimization strategies, and postoperative medical management plans ensures seamless transitions of care and reduces the likelihood of perioperative complications related to communication failures.

Table 2 summarizes key concepts related to preoperative patient preparation.

CONCLUSION

Multidisciplinary preoperative preparation is essential to ensure safe and effective surgical care, particularly for patients with complex comorbidities. Optimization of risk factors—including anemia, malnutrition, cardiopulmonary disease, and lifestyle-related factors—reduces perioperative complications, improves recovery, and, in high-risk populations, decreases mortality. Inadequate preparation or delayed optimization increases surgical risk, prolongs hospitalization, and disrupts healthcare efficiency. Active collaboration between family physicians, anesthesiologists, and surgical teams enhances risk stratification, patient readiness, and continuity of care. Structured, standardized, and patient-centered preoperative pathways are therefore critical to improving surgical outcomes and overall perioperative safety.

Financial Support: This research received no external funding or sponsorship.

Conflict of Interest Statement: The authors declare that there is no conflict of interest related to this paper.

Author Contribution & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript.

Note: Artificial intelligence is used to increase readability.

Sažetak

POVEZIVANJE PRIMARNE ZDRAVSTVENE ZAŠTITE I HIRURGIJE: ULOGA OPŠTIH LEKARA I ANESTEZIOLOGA U PERIOPERATIVNOJ OPTIMIZACIJI

Domi Rudin, Kaci Myzafer

Medicinski fakultet Univerziteta u Tirani, Katedra za hirurgiju, Tirana, Albanija

Prelazak pacijenta iz primarne zdravstvene zaštite ili iz internističkog sektora u operacionu salu predstavlja ključnu fazu u perioperativnom menadžmentu. Hirurški pacijenti kojima je potrebna anestezija moraju proći sveobuhvatnu, multidisciplinarnu pripremu koja uključuje porodične lekare, interniste, hospitaliste, anesteziologe, hirurge i fizioterapeute. Ovaj multidimenzionalni pristup pomaže da prelazak na anesteziju i hirurgiju bude siguran i neometan, čime se optimizuju ishodi procedura. Ključni izazovi u ovoj fazi uključuju preciznu procenu fizikalnog statusa pacijenta, stratifikaciju rizika, optimizaciju komorbiditeta i upravljanje hroničnim lekovima. Adekvatna preoperativna priprema smanjuje rizik od odlaganja operacije i povećava bezbednost pacijenta. Ovaj rad ima za cilj da istakne ključna pitanja koja se mogu rešavati u saradnji lekara opšte prakse i anesteziologa, podstičući bolju komunikaciju, deljenje znanja i kliničku stručnost.

Ključne reči: perioperativna medicina, anestezija, hirurgija, hronični lekovi, komorbiditeti, perioperativna stratifikacija rizika.

REFERENCES

1. Tote SP, Grounds RM. Performing perioperative optimization of the high-risk surgical patient. Br J Anaesth. 2006; 97(1): 4-11. doi: 10.1093/bja/ael102.

2. Adesanya AO, Joshi GP. Comparison of knowledge of perioperative care in primary care residents versus anesthesiology residents. Proc (Bayl Univ Med Cent). 2006; 19(3): 216-20. doi: 10.1080/08998280.2006.11928165.

3. Majumdar JR, Forrester JW, Haviland KS, Massaro CD, Welch JC, Kelleher DC. PrEP-ared for surgery? A comprehensive narrative review of perioperative recommendations for anesthesia providers. AANA J. 2025; 93(5): 353-62. doi: 10.70278/AANAJ/.0000001034.

4. Sun Y, Chai F, Pan C, Romeiser JL, Gan TJ. Effect of perioperative goal-directed hemodynamic therapy on postoperative recovery following major abdominal surgery-a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2017; 21(1): 141. doi: 10.1186/s13054-017-1728-8.

5. Li N, Liu X, Wang Y, Song R, Xie X. Multimodal prehabilitation is an effective strategy to reduce postoperative complications and improve physical function and anxiety in patients with colorectal cancer undergoing elective surgery: a systematic review and network meta-analysis. Front Med (Lausanne). 2025; 12: 1619959. doi: 10.3389/fmed.2025.1619959.

6. Knight SR, Qureshi AU, Drake TM, Lapitan MCM, Maimbo M, Yenli E, et al. The impact of preoperative oral nutrition supplementation on outcomes in patients undergoing gastrointestinal surgery for cancer in low- and middle-income countries: a systematic review and meta-analysis. Sci Rep. 2022; 12(1): 12456. doi: 10.1038/s41598-022-16460-4.

7. Lai WY, Chiu YC, Lu KC, Huang IT, Tsai PS, Huang CJ. Beneficial effects of preoperative oral nutrition supplements on postoperative outcomes in geriatric hip fracture patients: A PRISMA-compliant systematic review and meta-analysis of randomized controlled studies. Medicine (Baltimore). 2021; 100(47): e27755. doi: 10.1097/MD.0000000000027755.

8. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg. 2015; 102(11): 1314-24. doi: 10.1002/bjs.9861.

9. Buhl H, Nørgaard A, Otkjaer A, Jørgensen LN, Jørgensen HL. The impact of anemia and blood transfusion on mortality after open abdominal surgery in the elderly. Langenbecks Arch Surg. 2023; 408(1): 421. doi: 10.1007/s00423-023-03122-w.

10. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO. Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. Am J Med. 2011; 124(2): 144-54.e8. doi: 10.1016/j.amjmed.2010.09.013.

11. Lenet T, Baker L, Park L, Vered M, Zahrai A, Shorr R, et al. A systematic review and meta-analysis of randomized controlled trials comparing intraoperative red blood cell trans-

fusion strategies. Ann Surg. 2022; 275(3): 456-66. doi: 10.1097/SLA.0000000000004931.

12. Knight JB, Subramanian H, Sultan I, Kaczorowski DJ, Subramaniam K. Prehabilitation of cardiac surgical patients, part 1: anemia, diabetes mellitus, obesity, sleep apnea, and cardiac rehabilitation. Semin CardiothoracVascAnesth. 2022; 26(4): 282-94. doi: 10.1177/10892532221121118.

13. Shanmugasundaram Prema S, Ganapathy D, Shanmugamprema D. Prehabilitation strategies: enhancing surgical resilience with a focus on nutritional optimization and multimodal interventions. Adv Nutr. 2025; 16(4): 100392. doi: 10.1016/j.advnut.2025.100392.

14. McIsaac DI, Abdulla K, Yang H, Sundaresan S, Doering P, Vaswani SG, et al. Association of delay of urgent or emergency surgery with mortality and use of health care resources: a propensity score-matched observational cohort study. CMAJ. 2017; 189(27): E905-12. doi: 10.1503/cmaj.160576.

15. Almonacid-Cardenas F, Rivas E, Auron M, Hu L, Wang D, Liu L, et al. Association between preoperative anemia optimization and major complications after non-cardiac surgery: a retrospective analysis. Braz J Anesthesiol. 2024; 74(2): 744474. doi: 10.1016/j.bjane.2023.11.004.

16. Committee on Standards and Practice Parameters; Apfelbaum JL, Connis RT, Nickinovich DG; American Society of Anesthesiologists Task Force on Preanesthesia Evaluation; Pasternak LR, et al. Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology. 2012; 116(3): 522-38. doi: 10.1097/ALN.0b013e31823c1067.

17. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014; 64(22): e77-137. doi: 10.1016/j.jacc.2014.07.944.

18. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The joint task force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014; 35(35): 2383-431. doi: 10.1093/eurheartj/ehu282.

19. Vetrugno L, Steinberg I, Colaianni-Alfonso N, Castro-Sayat M. Lung ultrasound score in postoperative pulmonary complications: predicting complications or over-complicating predictions? EurJAnaesthesiol. 2026; 43(1): 83-4. doi: 10.1097/EJA.0000000000002213. Epub 2025 Dec 10.

20. Qaseem A, Snow V, Fitterman N, Hornbake ER, Lawrence VA, Smetana GW, et al. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. Ann Intern Med. 2006; 144(8): 575-80. doi: 10.7326/0003-4819-144-8-200604180-00008.

21. Duggan EW, Carlson K, Umpierrez GE. Perioperative hyperglycemia management: an update. Anesthesiology. 2017; 126(3): 547-60. doi: 10.1097/ALN.0000000000001515.

22. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl): e326S-e350S. doi: 10.1378/chest.11-2298.

23. Tsokkou S, Konstantinidis I, Papakonstantinou M, Chatzikomnitsa P, Gkaitatzi AD, Liampou E, et al. Optimizing preoperative anemia in non-metastatic colorectal cancer: a systematic review on surgical recovery and outcomes. Cancers (Basel). 2025; 17(22): 3689. doi: 10.3390/cancers17223689.

24. Borgomoni GB, de Lima Júnior FAS, Mejia OAV, Jatene FB. The imperative integration of patient blood management into ERACS: bridging the gap for optimizing outcomes in cardiac surgery. Perioper Med (Lond). 2025; 14(1): 124. doi: 10.1186/s13741-025-00606-9.

Correspondence to/Autor za korespondenciju
Prof dr Rudin Domi
Department of Surgery, Faculty of Medicine, University of Medicine, Tirana, Albania
Email: rudin.domi@umed.edu.al
Mob: 00355682067003
ORCID: https://orcid.org/0000-0003-4594-7815

***How to cite this article**:* Domi R, Kaci M. Bridging Primary Care and Surgery: The Role of General Physicians and Anesthesiologists in Perioperative Optimization. Sanamed. 2025; 20(3): 287-293. doi: 10.5937/sanamed20-62422.

SANAMED
2025; 20(3): 295–300
ISSN-1452-662X

DOI: 10.5937/sanamed0-61606
UDK: 61:929 Кодман Е.А.; 613/614
ID: 183821065
Review article

THE LIFE AND LEGACY OF ERNEST AMORY CODMAN: A PIONEER OF OUTCOMES AND A FORERUNNER OF MODERN QUALITY MEASUREMENT SYSTEMS IN HEALTHCARE

Medarevic Aleksandar

Independent Researcher, Belgrade, Serbia

Primljen/Received: 20. 09. 2025. Prihvaćen/Accepted: 16. 11. 2025. Online First: 25. 11. 2025.

Abstract: Ernest Amory Codman (1869–1940) was an American surgeon, reformer, and visionary whose work marked the beginnings of systematic quality measurement in medicine. The first part of this paper traces his life and career: his education at Harvard Medical School, his work at Massachusetts General Hospital, his conflicts with colleagues over his insistence on public reporting of outcomes, his founding of a private hospital, and the establishment of the Bone Sarcoma Registry—one of the first disease-specific registries in history.

The second part of the paper analyzes his philosophy of the "End Result System" through a comparative table in which its core principles—patient monitoring, complication tracking, transparency, continuous improvement, and accountability—are compared with their modern equivalents, such as outcome indicators, national registries, public reporting systems, quality improvement (QI) methodologies, and health information systems.

The paper concludes that Codman's work represents both the biographical story of a persistent reformer and a conceptual foundation for modern quality measurement systems in healthcare.

Keywords: quality of health care, quality improvement, evidence-based practice, hospitals.

Ernest Amory Codman and his idea of the "End Result System"

The National Academy of Medicine of the United States of America defines the quality of healthcare as the extent to which healthcare services increase the likelihood of good outcomes and reduce the likelihood of harm for patients (1). The World Health Organization also frequently cites this definition of quality in its documents (1).

In modern public health practice, quality implies not only technical efficiency and professional competence, but also the structure of the system, the processes that are applied, and the outcomes that are achieved. In this context, Ernest Amory Codman stands out as one of the first to systematically insist on measuring treatment outcomes, analyzing errors, and making them publicly available.

Ernest Amory Codman was born into a Puritan family on December 30, 1869, in Boston, Massachusetts, USA. He entered Harvard College in 1887, graduating with honors four years later. He then enrolled at Harvard Medical School, where he met and became friends with Harvey Cushing, the future eminent neurosurgeon (2). Codman graduated in medicine in 1895 and immediately began working in the Department of Surgery at Massachusetts General Hospital (MGH).

He was the author of the first English-language textbook on X-ray photography techniques. In Serbian medical literature, he is best known for the "Codman sign," seen in rapidly growing bone tumors and other aggressive bone lesions (3). On an X-ray, this sign appears as a triangular shadow between the bone cortex and the elevated periosteum.

Codman also made a significant contribution to shoulder surgery. In 1931, he described "chondroblastoma," a rare benign bone tumor later referred to as the "Codman tumor" (4). He also introduced **Codman's exercises**—a set of movements for passive mobilization of the shoulder joint (5). These exercises involve the patient standing with the torso bent forward, while the affected arm hangs freely and moves gently back and forth or in circular motions, like a pendulum, without activating the shoulder girdle muscles. They remain integral to many rehabilitation protocols, especially in the United States.

At the time of Codman's work, no organized system for monitoring healthcare quality existed. Physicians and hospitals were not required to record treatment outcomes, much less analyze or publicly disclose them. Codman recognized that such a lack of accountability deprived patients of clear information regarding the safety and effectiveness of their treatment, while depriving healthcare professionals of feedback necessary for improvement.

He believed that systematic outcome measurement would identify best practices and eliminate "the lazy and ill-trained surgeons of your community, even though they hold high places" (6). He openly criticized nepotism and the practice of promotion based on seniority rather than merit, arguing that such systems perpetuated poor medical practice and turned it into dogma.

Through his revolutionary concept of the **"End Result System,"** Codman proposed that "[E]very hospital should follow every patient it treats long enough to determine whether or not the treatment has been successful," and then ask, "If not, why not?" (6). In essence, this meant:

• every patient deserves to know the final result of their treatment,

• every doctor should be willing to present their results to the public, and

• hospitals should be evaluated by the success of their treatments.

In practice, Codman used **"End Result Cards,"** measuring 12.5 × 20 cm, on which physicians recorded symptoms, initial diagnosis, treatment plan, complications, final diagnosis, and overall outcome—success or failure. He followed patients for at least a year after intervention. Codman publicly presented data on his deceased patients—141 cases—during his 15 years at MGH.

Codman was an uncompromising advocate of quality measurement, critical both of others and of himself. He called quality his "monomania" (7). In one report, after a failed operation, he candidly wrote:

"*I made an error of skill of the most gross character and even failed to recognize that I had made it.*" (6)

Although Codman's ideas are now widely accepted, they were highly controversial in his day. Many physicians felt that tracking errors undermined the profession's reputation and violated patients' trust. As a result, Codman was isolated and forced to leave MGH. Codman resigned from his job at MGH in 1911 to open his own hospital. He and his staff were able to track the status of every patient by implementing the "End Result System" in his own hospital, with between ten and twelve beds, demonstrating a commitment to the principle of accountability. Between 1911 and 1916, Codman recorded data on 337 patients at his own hospital and 123 "errors" or deficiencies in treatment (8). Determined to spread the word, Codman printed the results of two years of follow-up at his hospital— a rate of one complication for every three patients— and sent them to hospitals across the United States. In return, he asked for their complication rates. No one responded.

In his hospital, he further elaborated on the causes of adverse outcomes, classifying them into categories: "C" for accidents or causes beyond the operator's control; "P" for causes related to the patient and the patient's disease or unavoidable consequences of the disease; and "E" for error or preventable accident (9). He focused further on E errors, which he believed could be due to a lack of technical knowledge, skill, or surgical judgment, or diagnostic acumen on the surgeon's part. Errors due to equipment deficiencies were listed as institutional errors. This classification and accounts of his cases were published by Codman in his revolutionary study *A Study in Hospital Efficiency*, a book small in scope but of revolutionary contribution (8).

The real shock came in 1915 at a meeting of the Suffolk County Surgical Society (6). After a few lectures, Codman, as the section president, stepped onto the podium and revealed a cartoon he had commissioned. At the centre of the cartoon was an ostrich with its head buried in sand, surrounded by dozens of golden eggs it had laid. It represented the local surgical patients who, without the outcome-monitoring system he advocated, had enriched the MGH in blissful ignorance. It was the height of Codman's frustration. The drawing also featured the MGH board of directors, asking if they would stop laying golden eggs if they published "the truth about their patients." Those present could not believe their eyes. Codman had been considered a weirdo before, but the establishment couldn't get over the sting of such a slap in the face. Codman was asked to resign as president of the group. Doctors reduced the number of patients sent to his hospital, resulting in a nearly 40% drop in revenue over the next year.

Excommunicated by his former colleagues, he turned to other activities. He led Boston's medical relief teams in establishing an emergency surgical hospital that treated thousands of injured people after a catastrophic explosion when two ships collided in Halifax Harbor, killing and seriously injuring thousands of residents of the Canadian city. The makeshift hospital used "End Result Cards" for each patient. With the United States' entry into World War I, Codman became the senior surgeon for the defence of Delaware Harbor, spending much of his time dealing with influenza epidemics in his jurisdiction. The "End Result Hospital"

had fallen into disrepair in his absence. After the war ended, he returned to his closed hospital "in debt, unable to borrow, and somewhat disillusioned with the possibility of changing the ways of human nature" (3). Finally, the hospital had closed by June 1919.

Codman was not reinstated at MGH 14 years after his departure. He spent the postwar years developing the first disease registry. In one of his hundred papers, Codman described a method for tracking patients with criteria for reporting and the necessary information (10). He began his bone sarcoma registry in 1920 with a gift of $1,000 from a patient's family. Codman later received a grant from the American College of Surgeons (ACS). His first collaborators in analysing the data were pathologist James Ewing and surgeon Joseph Bloodgood (11). Codman, however, was not as successful in promoting it among his colleagues (12). Over the next six years, he collected data on only seventeen cases of sarcoma from other members of the association, which at that time had 7,000 members. The monograph resulting from the analysis of cases in the registry is the first attempt to standardize and disseminate the classification and nomenclature of a particular disease and the first estimate of the incidence of malignant diseases.

Direct results arising from the work on the registry are: longer follow-up of treated patients and calculation of multi-year survival rates; standardization of certain services (analysis of pathological material, radiographic diagnostics, etc.); promotion of national clinical research on a larger population through joint work of experts from different parts of the country; and creation of modern orthopaedics by linking pathology, radiology, and surgery.

Codman devoted the rest of his life to writing his autobiography, *The Shoulder* (13). For decades, this book was the textbook of shoulder orthopaedics in the United States. He continued to publish his results publicly each year, to the chagrin of his fellow surgeons who "spent their lives in the practice of the art of medicine rather than in that of the science, and, being financially successful, are able to influence the trustees of hospitals against analysis of the results; (and) comparison of achievements would be, to them, as odious as a comparison of incomes" (14).

The Shoulder was a textbook of the highest order, but for Codman it was a farewell letter for what he considered his most significant contribution to medicine. He prophetically pointed out that new generations would see the significance of the "End Result" approach, which "Harvard would claim as a jewel in her crown" (7). He suffered the fate of Ignaz Semmelweis (15). He died in 1940 of melanoma, in extreme poverty. He was buried in an unmarked grave, begging his wife to spend her savings on something more useful (16).

Main components and elements of Codman's idea with examples of modern implementation

Codman is one of the founders of the ACS, where he was the first head of the Department for Standardization (17). The Hospital Accreditation Program was developed in 1918 by this department, which later led to the creation of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). It was only after Codman's death that the idea of "quality care" became popular. Only under public pressure did JCAHO accept the need to study clinical outcomes as part of measuring the quality of care in the 1980s (18).

Implementation was challenging, however. Physicians and hospitals were reluctant to document clinical outcomes, citing various problems, including medico-legal, technical, or a lack of time (19)—excuses that are still used today. Under increasing pressure, JCAHO compromised by offering an alternative method that measured "quality" through "structure" and "process" (9). When it became apparent that poor clinical outcomes still occurred even when adequate "structures" (the existence of trained personnel and modern medical devices) and appropriate "processes" (clinical protocols, properly maintained medical records, etc.) were in place, advocates of the quality of care movement continued to fight.

Resistance from doctors and hospitals was so strong that the U.S. Congress eventually had to intervene, creating the Agency for Health Care Policy and Research (AHCPR) in 1989, whose primary mission was to conduct outcomes research and disseminate the results. The Agency's classification of medical errors is very similar to Codman's original classification (20). The establishment of this Agency was a triumph for Codman at the national level.

The Joint Commission established the **Ernest A. Codman Award** for using outcome measures to improve the quality and safety of patient care (21). The ACS website contains an online tool for estimating the likelihood of an unfavourable outcome (such as complications or death) after surgery, using information that the patient provides to the health care provider about their previous health history (22). Today, MGH has the **Edward P. Lawrence Centre for Quality and Safety**, which has been working since 2008 to improve the culture of quality at MGH and among members of the Massachusetts General Practitioners Association (23). With donations from the ACS, JCAHO, MGH, the Association of Shoulder and Elbow Surgeons, and an individual donor, a bust with his image in bas-relief was erected in 2014 (3).

Donabedian's quality model (structure–process–outcome) also builds on Codman's ideas (7). Most countries now have patient safety programs that require hospitals to track and report medical errors. These programs include the work of special teams composed of hospital management, administrative, and medical staff—exactly the type of interdisciplinary collaboration Codman advocated. Codman's systematic collection of data on bone sarcoma initiated the creation of disease-specific registries, allowing for outcome tracking in specific conditions. Whether good or bad, reporting on actual health outcomes is now a common practice in most developed healthcare systems. Codman's vision of quality in healthcare consisted of several key elements later developed into modern equivalents. Some of those equivalents are summarized in Table 1.

Europe has lagged behind the USA in adopting the quality philosophy. The same applies to present-day Serbia, where monitoring the quality of health care officially began in 2004, when the Ministry of Health published a document titled *Instruction on Monitoring the Quality of Work in Healthcare Institutions* as part of the program *Monitoring the Quality of Work in Healthcare Institutions in the Republic of Serbia* (24). In this regard, the Agency for Accreditation of Healthcare Institutions of Serbia and the Accreditation Body of Serbia were established. Unfortunately, studies on the effectiveness of accreditation on final outcomes are scarce, and the results published so far are contradicto-

Table 1. *Key elements of Codman's philosophy and their modern equivalents in healthcare quality*

Element	**What does it mean in practical terms?**	**Modern equivalents/correlations**
Patient follow-up	Monitor the patient after treatment to see if there has been a complete recovery and healing without complications or disability.	Outcome measures: recurrence, functionality, quality of life, mortality; disease registries; satisfaction with healthcare; clinical follow-up in RCTs and cohort studies.
Failure/complication records	Codman recorded all cases where treatment did not achieve the desired result and tried to determine why.	Morbidity and complications rate as standards in surgical reports; conferences on morbidity & mortality; root-cause analysis; clinical audit.
Objectivity and transparency	He wanted the results to be available, to know the errors, and to compare surgeons and hospitals.	Informed patient consent; public reporting of outcomes; licensing;(hospital) accreditation system; transparent recruitment of staff; national registries; online platforms with hospital comparisons; various lists of "best" hospitals at the national or global level
Continuous improvement	After identifying errors or failures, analyse why and implement improvement measures.	Efficiency; functional differentiation of hospitals, quality improvement (QI); PDCA / PDSA cycles; lean, six sigma NSQIP; patient safety programs; treatment process indicators (e.g. time to intervention, average length of hospitalization); healthcare worker satisfaction; hospital action plans; evidence-based medicine; continuing medical education; anaesthesia information management system (AIMS); quality management (QM)
Accountability	Doctors and hospitals should be held accountable for treatment outcomes; their work should be evaluated and criticized when unsuccessful.	Regulatory agencies; health care contracting; peer review; quality-based payment systems;case-mix, diagnostically related groups

ry (25). After several decades, the chambers of healthcare professionals were renewed (24). The challenges present in Codman's time still exist in today's Serbia, a century after the publication of *A Study in Hospital Efficiency*.

CONCLUSION

Ernest Amory Codman is one of the most significant figures in the history of modern medicine, whose vision far exceeded his time. His books hold the same importance for modern medicine as the *Corpus Hippocraticum*. His *End Result System* concept was the first systematic attempt to introduce the measurement of treatment outcomes as the foundation for improving quality and accountability in health care and medicine.

Although his ideas initially met with strong resistance, today they represent the foundation on which hospital accreditation programs, national and international disease registries, public outcome reporting systems, and patient safety initiatives are based. His work remains a powerful reminder that transparency, outcome monitoring, and continuous quality improvement are essential for the progress of medicine.

Modern quality measurement systems in health care cannot be understood without insight into Codman's philosophy, making him a pioneer and a turning point in the development of health quality improvement.

Abbreviations

USA – United States of America

ACS – American College of Surgeons

JCAHO – Joint Commission on Accreditation of Healthcare Organizations (now *The Joint Commission*)

AHCPR – Agency for Health Care Policy and Research (now *AHRQ – Agency for Healthcare Research and Quality*)

RCT – Randomized Controlled Trial

QI – Quality Improvement

PDCA / PDSA – Plan–Do–Check–Act / Plan–Do–Study–Act

NSQIP – National Surgical Quality Improvement Program (ACS program)

AIMS – Anesthesia Information Management System

QM – Quality Management

Conflict of Interest: The author declares no conflicts of interest related to this article.

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

Source of Funding: The author declares that he did not receive any funds or support for this study from public, private, or nonprofit funding organizations.

Sažetak

ŽIVOT I NASLEĐE ERNESTA AMORIJA KODMANA: PIONIRA ISHODA I PRETEČE MODERNIH SISTEMA MERENJA KVALITETA U SISTEMU ZDRAVSTVENE ZAŠTITE

Medarevic Aleksandar

Nezavisni istraživač, Beograd, Srbija

Ernest Amori Kodman (1869–1940) bio je američki hirurg, reformator i vizionar čiji je rad označio početak sistematskog merenja kvaliteta u medicini. Prvi deo rada prati njegov životni put: njegovo obrazovanje na Medicinskom fakultetu Harvard, njegov rad u Opštoj bolnici Masačusets, njegove sukobe sa kolegama zbog insistiranja na javnom izveštavanju o ishodima, osnivanje sopstvene bolnice i razvoj Registra sarkoma kostiju kao prvog registra specifične bolesti. Drugi deo rada analizira njegovu filozofiju „Sistema krajnjih rezultata" kroz uporednu tabelu u kojoj se osnovni principi (praćenje pacijenata, evidencija komplikacija, transparentnost, kontinuirano poboljšanje i odgovornost) upoređuju sa savremenim ekvivalentima, kao što su indikatori ishoda, nacionalni registri, sistemi javnog izveštavanja, metodologije poboljšanja kvaliteta i informacioni sistemi. U radu se zaključuje da je Kodmanovo delo i biografska priča o upornom reformatoru i analitička osnova za moderne sisteme kvaliteta u sistemu zdravstve zaštite.

Ključne reči: kvalitet zdravstvene zaštite, unapređenje kvaliteta, praksa zasnovana na dokazima, bolnice.

REFERENCE

1. Mosadeghrad AM. Healthcare service quality: towards a broad definition. Int J Health Care Qual Assur. 2013; 26(3): 203-19. doi:10.1108/09526861311311409

2. Brand RA. Ernest Amory Codman, MD, 1869-1940. Clin Orthop Relat Res. 2009; 467(11): 2763-5. doi:10.1007/s11999-009-1047-8.

3. Nakayama DK. Ernest Amory Codman and the End Result Idea in surgical quality. Am Surg. 2023; 89(11): 4237-40. doi:10.1177/00031348221148344.

4. Codman EA. The Classic: Epiphyseal chondromatous giant cell tumors of the upper end of the humerus. Surg Gynecol Obstet.1931;52:543. Clin Orthop Relat Res. 2006; 450: 12-6. doi: 10.1097/01.blo.0000229309.90265.df.

5. Cunningham G, Charbonnier C, Ladermann A, Chague S, Sonnabend DH. Shoulder motion analysis during Codman pendulum Eexercises. Arthrosc Sports Med Rehabil. 2020; 2(4): e333-e9. doi: 10.1016/j.asmr.2020.04.013.

6. The Codman Affair 2015 [updated 2015-09-15. Available from: https://protomag.com/policy/the-codman-affair/.

7. Donabedian A. The end results of health care: Ernest Codman's contribution to quality assessment and beyond. Milbank Q. 1989; 67(2): 233-56; discussion 57-67.

8. Codman EA. The classic: A study in hospital efficiency: as demonstrated by the case report of first five years of private hospital. Clin Orthop Relat Res. 2013; 471(6): 1778-83. doi: 10.1007/s11999-012-2751-3

9. Margo C. Ernest A. Codman and the idea of medical accountability. Hektoen International a Journal of Medical Humanities. 2024.

10. Codman EA. The classic: the registry of bone sarcomas as an example of the end-result idea in hospital organization. 1924. Clin Orthop Relat Res. 2009; 467(11): 2766-70. doi: 10.1007/s11999-009-1048-7

11. McCarthy EF. The registry of bone sarcoma. a history. Iowa Orthop J. 1995; 15:74-8.

12. Codman E. The registry of bone sarcoma and medical human nature. Boston Med Surg. 1922; 187 :208-11. doi: 10.1056/NEJM192208101870608.

13. Gainty C. The autobiographical Shoulder of Ernest Amory Codman: crafting medical meaning in the twentieth century. Bull Hist Med. 2016; 90(3): 394-423. doi: 10.1353/bhm.2016.0071.

14. DePalma AF. Foreword - Codman [2025-09-20]. Available from: https://shoulderdoc.co.uk/pages/foreword-codman.

15. Paul S, Salunkhe S, Sravanthi K, Mane SV. Pioneering hand hygiene: Ignaz Semmelweis and the fight against puerperal fever. Cureus. 2024; 16(10): e71689. doi: 10.7759/cureus.71689

16. Mallon B. Ernest Amory Codman: the end result of a life in medicine: Saunders; 2000.

17. Neuhauser D. Ernest Amory Codman, M.D., and end results of medical care. Int J Technol Assess Health Care. 1990; 6(2): 307-25. doi: 10.1017/s0266462300000842.

18. Patterson CH. Joint commission on accreditation of healthcare organizations. Infect Control Hosp Epidemiol. 1995; 16(1): 36-42. doi: 10.1086/647001.

19. Berwick DM. EA Codman and the rhetoric of battle: a commentary. The Milbank Quarterly. 1989; 67(2): 262-7. doi: 10.2307/3350141.

20. Gleason KM, McDaniel MR, Feinglass J, Baker DW, Lindquist L, Liss D, et al. Results of the medications at transitions and clinical handoffs (MATCH) study: an analysis of medication reconciliation errors and risk factors at hospital admission. J Gen Intern Med. 2010; 25(5): 441-7. doi: 10.1007/s11606-010-1256-6.

21. Noble J. The Codman competition: Rewarding excellence in performance measurement, 19 -20. Jt Comm J Qual Patient Saf. 2006; 32(11): 634-40. doi: 10.1016/s1553-7250(06)32082-x.

22. Goodwin AM, Kurapaty SS, Inglis JE, Divi SN, Patel AA, Hsu WK. A meta-analysis of the American college of surgeons risk calculator's predictive accuracy among different surgical sub-specialties. Surg Pract Sci. 2024; 16: 100238. doi: 10.1016/j.sipas.2024.100238.

23. Mort EA, Demehin AA, Marple KB, McCullough KY, Meyer GS. Setting quality and safety priorities in a target-rich environment: an academic medical center's challenge. Acad Med. 2013; 88(8): 1099-104. doi: 10.1097/ACM.0b013e31829a3ee8.

24. Roberta M, Radulović O, Ignjatović A, Stojanović M, Višnjić A. Quality of healthcare in the Republic of Serbia: The concept we still strive for. Glasnik javnog zdravlja. 2022; 96(1): 71-7. doi: 10.5937/serbjph2201071M.

25. Markovic Petrovic G, Vuković M, Jovic Vraneš A. The impact of accreditation on health care quality in hospitals. Vojnosanitetski pregled. 2018; 75(8): 803-8. doi: 10.2298/VSP160728390M.

Correspondence to/Autor za korespondenciju
Aleksandar Medarevic
Str Šajkaška 23, 11000 Belgrade, Serbia
email: aco.batut@gmail.com
Orcid Id: 0000-0002-7483-3625

***How to cite this article**:* Medarevic A. The life and legacy of Ernest Amory Codman: a pioneer of outcomes and a forerunner of modern quality measurement systems in healthcare. Sanamed. 2025; 20(3): 295-300. doi: 10.5937/sanamed0-61606.

UPUTSTVO AUTORIMA

Časopis **SANAMED** je međunarodni, recenzirani, multidisciplinarni medicinski časopis otvorenog pristupa, osnovan 2006. godine, a izdaje ga Udruženje lekara Sanamed, neprofitna organizacija lekara i naučnika. Časopis objavljuje: originalne članke, prikaze slučajeva, preglede literature, članke o istoriji medicine, članke za praktičare, prikaze knjiga, komentare i pisma uredniku i druge medicinske informacije posvećene unapređenju medicinskih istraživanja, praksi i obrazovanju, iz oblasti medicine i srodnih oblasti.

Časopis izlazi u elektronskom i štampanom formatu, tri puta godišnje. Odmah nakon objavljivanja, svi radovi su besplatno dostupni online, na web stranici časopisa i drugim bazama podataka.

Molimo autore da dostave, potpisane od svih autora, formulare Author statement, Patient consent, and Conflict of interests prilikom prilaganja članka (https://new.sanamed.rs/).

Od februara 2022. časopis Sanamed počeo je sa korišćenjem ASSISTANT sistema za elektronsko uređivanje časopisa. Svi korisnici sistema: autori, recenzenti i urednici moraju biti registrovani sa jedinstvenom email adresom. Za registraciju idite na https://aseestant.ceon.rs/index.php/sanamed/about/submissions.

Rukopisi se dostavljaju u elektronskoj formi putem ASSISTANT sistema.

Radovi se uvek dostavljaju sa sažetkom na engleskom i srpskom jeziku. Strani autori podnose radove samo na engleskom jeziku. Za nazive lekova isključivo se koriste generički nazivi. Uređaji (aparati, instrumenti) se nazivaju trgovačkim nazivima, a njihov naziv i mesto proizvodnje treba navesti u zagradama. Ako se koristi kombinacija slovo-broj, broj treba precizno označiti superskriptom ili indeksom (tj. 99Tc, IL-6, O2, B12, CD8). Ako se nešto obično piše kurzivom, kao što su geni (npr. BRCA1), to bi trebalo na ovaj način pisati i u radu.

Ako je rad deo magistarske ili doktorske teze, ili istraživačkog projekta, to treba navesti u posebnoj napomeni na kraju teksta. Takođe, ako je članak prethodno predstavljen na nekom naučnom skupu, potrebno je navesti naziv, mesto i vreme održavanja skupa, kao i način na koji je rad objavljen (npr. promenjen naslov ili sažetak).

IZJAVA O SUKOBU INTERESA. Rukopis mora biti propraćen izjavom o sukobu interesa svih autora u kojoj se izjašnjava o potencijalnom interesu ili navodi da autori nemaju sukob interesa. Obrazac izjave o sukobu interesa mora biti potpisan od strane svih autora i dostavljen uz rukopis.

AUTORSTVO. Svi pojedinci navedeni kao autori trebaju biti kvalifikovani za autorstvo. Svaki autor je trebao dovoljno sudelovati u pisanju članka kako bi preuzeo odgovornost za celi članak i rezultate prikazane u tekstu. Autori trebaju priložiti opis doprinosa svakog koautora pojedinačno (na kraju teksta).

PLAGIJAT. Svi rukopisi se proveravaju na plagijarizam (softver iThenticate).

OPŠTA UPUTSTVA

Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

Rukopis mora biti organizovan na sledeći način: naslovna strana, sažetak na srpskom jeziku, sažetak na engleskom jeziku, ključne reči, uvod, cilj rada, bolesnici i metodi/materijal i metodi, rezultati, diskusija, zaključak, literatura, tabele, legende za slike i slike.

Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

Obim rukopisa. Celokupni rukopis rada, koji čine naslovna strana, kratak sadržaj, tekst rada, spisak literature, svi prilozi, odnosno potpisi za njih i legenda (tabele, slike, grafikoni, sheme, crteži), naslovna strana i sažetak na engleskom jeziku, mora iznositi za originalni rad, saopštenje, rad iz istorije medicine i pregled literature do 5.000 reči, a za prikaz bolesnika, rad za praksu, edukativni članak do 3.000 reči; radovi za ostale rubrike moraju imati do 1.500 reči.

Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

Sva merenja, izuzev krvnog pritiska, moraju biti izražena u internacionalnim SI jedinicama, a ako je neophodno, i u konvencionalnim jedinicama (u zagradi). Za lekove se moraju koristiti generička imena. Zaštićena imena se mogu dodati u zagradi.

Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 400 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

Za slike koje su ranije već objavljivane treba navesti tačan izvor, treba se zahvaliti autoru, i treba priložiti pismeni pristanak nosioca izdavačkog prava da se slike ponovo objave.

Pisma uredniku. Mogu se publikovali pisma uredniku koja se odnose na radove koji su objavljeni u SANAMEDU, ali i druga pisma. Ona mogu sadržati i jednu tabelu ili sliku, i do pet referenci.

Propratno pismo. Uz rukopis obavezno priložiti pismo koje su potpisali svi autori, a koje treba da sadrži: izjavu da rad prethodno nije publikovan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu, te izjavu da su rukopis pročitali i odobrili svi autori koji ispunjavaju merila autorstva. Takođe je potrebno dostaviti kopije svih dozvola za: reprodukovanje prethodno objavljenog materijala, upotrebu ilustracija i objavljivanje informacija o poznatim ljudima ili imenovanje ljudi koji su doprineli izradi rada.

Troškovi pripreme rada

Svi autori radova, imaju obavezu da pre nego što dobiju potvrdu da će rad biti objavljen u Sanamedu, izvrše uplatu za pokriće dela troškova štampe koja za autora rada iznosi 2500 dinara, a za koautore po 1500 dinara, za svaki prihvaćeni rad. Za autora rada iz inostranstva naknada za štampanje iznosi 40 eura (u dinarskoj protivrednosti po kursu na dan uplate), a za koautore 20 eura. Dodatno će biti naplaćena svaka stranica na kojoj se nalaze slike u boji, po ceni od 30 eura; crno bele slike se ne naplaćuju.

Za sva dalja uputstva i informacije kontaktirajte Uredništvo.

Napomena. Rad koji ne ispunjava uslove ovog uputstva ne može biti upućen na recenziju i biće vraćen autorima da ga dopune i isprave. Pridržavanjem uputstva za pisanje rada za SANAMED znatno će se skratiti vreme celokupnog procesa do objavljivanja rada u časopisu, što će pozitivno uticati na kvalitet i redovnost izlaženja svezaka.

INSTRUCTIONS TO AUTHORS

SANAMED journal is international, peer-reviewed, multidisciplinary open-access medical journal, founded in 2006 and is published by the Association of medical doctors Sanamed, a nonprofit organization of physicians and scientists. The journal publishes: original articles, case reports, literature reviews, Systematic review, articles on history of medicine, articles for practitioners, book reviews, comments and letters to editor, and other medical information dedicated to the advancement of medical research, practice, and education, in the field of medicine and related fields.

The journal is published both in electronic and print format, three times a year. Immediately after publication, all papers are available online for free, on the journal's website and other databases.

IMPORTANT. Authors please fill out Author statement, Patient consent, and Conflict of interests forms when submitting your article (https://new.sanamed.rs/).

From February 2022, Sanamed journal started using electronic journal management editing via the ASSISTANT system. All users of the system: authors, reviewers and editors must be registered with a unique email address. To register go to https://aseestant.ceon.rs/index.php/sanamed/about/submissions.

Manuscripts are submitted in electronic form via ASSISTANT system.

The papers are always submitted with Abstract in both English and Serbian, included in the manuscript file. Foreign authors submit papers only in English Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CONFLICT OF INTEREST STATEMENT. The manuscript must be accompanied by a disclosure statement from all authors declaring any potential interest or stating that the authors have no conflict of interest. Conflict of interest statement form must be signed by all authors and submitted with manuscript.

AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text..The authors should enclose the description of contribution to the article of every co-author individually (at the end of the manuscript).

PLAGIARISM. All manuscripts have been submitted to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control.

GENERAL GUIDELINES

Text of the paper should be typed in a word processing program *Word*, written in Latin, double-spaced, only in *Times New Roman* font size 12 points. All margins should be set at 25 mm, and the text should be typed with the left alignment and paragraph indentations of 10 mm, without dividing the words.

The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

Manuscript volume. The complete manuscript, which includes title page, short abstract, text of the article, literature, all figures and permisions for them and legends (tables, images, graphs, diagrams, drawings),

title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

The word count check in a document can be done in *Word* processor program in submenu *Tools Word Count* or *File Properties Statistics*.

All measurements, except blood pressure, are reported in the System International (SI) and, if necessary, in conventional units (in parentheses). Generic names are used for drugs. Brand names may be inserted in parentheses.

Title page. The title page contains the title, short title, full names of all the authors, names and full location of the department and institution where work was performed, acknowledgments, abbreviations used, and name of the corresponding author. The title of the article is concise but informative, and it includes animal species if appropriate. A subtitle can be added if necessary.

A short title of less than 50 spaces, for use as a running head, is included.

A brief acknowledgment of grants and other assistance, if any, is included.

A list of abbreviations used in the paper, if any, is included. List abbreviations alphabetically followed by an explanation of what they stand for. In general, the use of abbreviations is discouraged unless they are essential for improving the readabillity of the text.

The name, telephone number, fax number, and exact postal address of the author to whom communications and reprints should be sent, are typed at the lower right corner of the title page.

Abstract page. An abstract of less than 400 words concisely states the objective, findings, and conclusion of the studies described in the manuscript. The abstract does not contain abbreviations, footnotes or references.

Below the abstract, 3 to 8 keywords or short phrases are provided for indexing purposes.

The structure of work. All headings are written in capital letters and bold.

Original work should have the following headings: introduction, aim, methods, results, discussion, conclusion, references.

A case report include: introduction, case report, discussion, references.

Review of the literature include: an introduction, subheadings, conclusion, references.

Patients and methods/Material and methods. The selection of patients or experimental animals, including controls is described. Patients' names and hospital numbers are not used.

Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

When reporting experiments on human subjects, it should be indicated whether the procedures followed were in accordance with ethical standards of the Committee on human experimentation of the institution in which they were done and in accordance with the Declaration of Helsinki. Hazardous procedures or chemicals, if used, are described in detail, including the safety precautions observed. When appropriate, a statement is included verifying that the care of laboratory animals followed the accepted standards.

Statistical methods used, are outlined.

Results. Results are clear and concise, and include a minimum number of tables and figures necessary for proper presentation.

Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

References. References are identified in the text by Arabic numerals in parentheses. They are numbered consecutively in the order in which they appear in the text. Number of references should not exceed 30, except in the literature review, which is allowed to be to 50.

Avoid using abstracts as references and abstract older than two years are not cited.

References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

Tables. Tables are typed on separate sheets with figure numbers (Arabic) and title above the table and explanatory notes, if any, below the table.

Figures and figure legends. All illustrations (photographs, graphs, diagrams) are to be considered figures, and are numbered consecutively in the text and figure legend in Arabic numerals. The number of figures included is the least required to convey the message of the paper, and no figure duplicates the data presented in the tables or text. Letters, numerals and symbols must be clear, in proportion to each other, and large enough to be readable when reduced for publication. Figures are submitted as near to their printed size as possible. Legends for figures should be given on separate pages.

If magnification is significant (photomicrographs), it is indicated by a calibration bar on the print, not by a magnification factor in the figure legend. The length of the bar is indicated on the figure or in the figure legend.

Photographs of identifiable patients are accompanied by written permission from the patient.

For figures published previously, the original source is acknowledged, and written permission from the copyright holder to reproduce it is submitted.

Letters to the Editor. Both letters concerning and those not concerning the articles that have been published in SANAMED will be considered for publication. They may contain one table or figure and up to five references.

Cover letter. The letter signed by all authors must be attached with the manuscript. The letter should consist of: the statement that the paper has not been published previously and that it is not submitted for publication to some other journal, the statement that the manuscript has been read and approved by all the authors who fulfill the authorship criteria. Furthermore, authors should attach copies of all permits: for reproduction of previously published materials, for use of illustrations and for publication of information about publicly known persons or naming the people who contributed to the creation of the work.

Costs of paper preparation

All authors of papers, have obligation, before they receive confirmation that the paper will be published in Sanamed, to pay part of expenses of printing, which is 2500 RSD for author, 1500 RSD for co-authors, for each paper.

For paper author from abroad printing fees are 40 Euro (in Dinar equivalent at the exchange rate on the day of payment), and 20 Euro for co-authors. Additionally will be charged each page with pictures in color, costing 30 Euro; black and white pictures will not be charged.

For any further instructions and information, contact Editorial Board.

Note. The paper which does not fulfill the conditions set in this instruction cannot be set to reviewers and will be returned to the authors for amendments and corrections. By following the instructions for writing the papers for Medical Journal, the time needed for the process of publication of papers in the journal will be shortened, which will have positive impact on the quality and regularity of publication of volumes.

CIP — Каталогизација у публикацији
Народна библиотека Србије, Београд

61

SANAMED : medical journal / glavni i odgovorni urednici Džemail Detanac, Massimo Sartelli, Demet Sengul. — God. 1, br. 1 (2006)– . — Novi Pazar : Udruženje lekara „Sanamed“, 2006– (Kraljevo : Ofset). — 30 cm

Tri puta godišnje. — Tekst na engl. jeziku. — Drugo izdanje na drugom medijumu: Sanamed (Online) = ISSN 2217-8171

ISSN 1452-662X = Sanamed

COBISS.SR-ID 135154444

ISSN 1452-662X