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Med Pregl 2026; LXXIX(1-2): 5-6. Novi Sad: januar-februar.

LETTERS TO EDITORIAL BOARD
PISMA UREDNIŠTVU

Dear Colleagues,

It is my pleasure to introduce the first issue of Medical Review for 2026, which brings together contributions addressing important contemporary challenges in clinical medicine, surgery, rehabilitation, reproductive medicine, and translational research. The articles included in this issue reflect the growing importance of multidisciplinary collaboration, personalized treatment strategies, and the integration of emerging technologies into everyday clinical practice.

The issue opens with an *editorial* by **Mobasheri**, who discusses the transition from consensus-based recommendations toward real-world implementation of personalized osteoarthritis care. The author emphasizes the need for phenotypic stratification, multimodal management, and patient-centered approaches in order to overcome the limitations of traditional "one-size-fits-all" therapeutic models. This contribution highlights the future direction of osteoarthritis management, integrating precision medicine, multidisciplinary care, and research equity into routine clinical practice [1].

Among the *original studies*, **Nikolić et al.** present a comprehensive 15-year analysis of groin wound infections following femoral vascular access procedures in a tertiary vascular center. Their findings demonstrate a persistently high incidence of surgical site infections and a concerning increase in methicillin-resistant Staphylococcus aureus over time, underscoring the importance of ongoing epidemiological surveillance and institutional antimicrobial stewardship strategies [2].

The prospective observational study by **Belopavlović et al.** evaluates pain assessment after gastrointestinal endoscopic procedures in pediatric patients. By focusing on the subjective experience of pain and procedural tolerance in children, the authors emphasize the importance of age-appropriate assessment tools and individualized perioperative care in pediatric gastroenterology [3].

Another important vascular surgery contribution comes from **Budinski et al.**, who analyze outcomes and complications of open carotid artery revascularization in relation to the clinical presentation of disease. Their results provide clinically relevant insights into perioperative risk stratification and highlight the continued importance of surgical expertise in the treatment of carotid artery pathology [4].

The study by **Batinić et al.** investigates perioperative outcomes after open surgical repair of symptomatic non-ruptured abdominal aortic aneurysm. The authors demonstrate the complexity of managing these high-risk patients and emphasize the significance of careful preoperative evaluation and perioperative optimization in improving surgical outcomes [5].

In the *review article*, **Uram Dubovski et al.** discuss preoperative considerations and the most common non-obstetric surgical conditions encountered during pregnancy. This comprehensive overview addresses diagnostic challenges, anesthetic considerations, and surgical timing, highlighting the importance of multidisciplinary cooperation between surgeons, obstetricians, anesthesiologists, and neonatologists in achieving optimal maternal and fetal outcomes [6].

Within the *Seminar for Physicians* section, **Bjelica et al.** provide an overview of current applications of artificial intelligence in *in vitro* fertilization. The authors discuss the growing role of machine learning and automated image analysis in embryo selection, treatment optimization, and reproductive outcome prediction, while also critically addressing current limitations and ethical considerations associated with the use of artificial intelligence in reproductive medicine [7].

Among the *case reports*, **Vlačić et al**. describe the non-specific clinical manifestation of nodular cutaneous melanoma. This report highlights the diagnostic difficulties associated with atypical dermatologic presentations and emphasizes the importance of maintaining a high index of suspicion for malignant skin lesions in everyday clinical practice [8].

Finally, **Lazin et al.** present a series of cases in which exacerbation of chronic obstructive pulmonary disease represented the initial manifestation of lung carcinoma. These cases underscore the importance of careful diagnostic evaluation in patients with atypical or treatment-resistant respiratory symptoms, particularly in populations at increased oncological risk [9].

We hope that the contributions presented in this issue will stimulate further research, support evidence-based clinical decision-making, and encourage interdisciplinary collaboration across multiple fields of medicine. I would like to sincerely thank all authors, reviewers, and members of the editorial board for their continued dedication to the journal and to the advancement of medical science.

With kind regards,

Radmila Matijević
Editor-in-Chief, Medical Review

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EDITORIAL
UVODNIK

FROM TREATMENT GUIDELINES AND CONSENSUS STATEMENTS TO REAL-WORLD IMPLEMENTATION – TRANSFORMING OSTEOARTHRITIS CARE THROUGH PHENOTYPIC STRATIFICATION AND MULTIDISCIPLINARY MANAGEMENT

OD SMERNICA ZA LEČENJE I IZJAVA O KONSENZUSU DO PRIMENE U STVARNOM SVETU – TRANSFORMISANJE LEČENJA OSTEOARTRITISA FENOTIPSKOM STRATIFIKACIJOM I MULTIDISCIPLINARNIM PRISTUPOM

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Editorial
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Introduction

Osteoarthritis (OA) is the most prevalent and disabling form of arthritis worldwide [1–3]. The current OA management landscape is characterized by a significant discordance between guideline recommendations and their implementation in primary care. Although numerous clinical practice guidelines exist [4–6], they often contain subtle inconsistencies and, more importantly, fail to adequately account for the substantial heterogeneity and multimorbidity that characterize the OA population [7]. Phenotypic heterogeneity in OA [8,9] manifests across multiple domains, including structural, inflammatory, metabolic, and pain-related pathways. This diversity is primary key reason why single-agent or unimodal treatments frequently fail to provide satisfactory outcomes, contributing to patient dissatisfaction and placing and increasing and unsustainable burden on primary healthcare systems [10]. To address these challenges, the OA research and clinical development communities must shift toward therapeutic strategies that are both multimodal in application and stratified in design, while also prioritizing research equity with respect to sex [11,12], race, and geographical diversity [13].

The Inadequacies of Unimodal Care

The complexity of OA-related pain, particularly in moderate to severe knee OA, underscores the limitations of traditional single-intervention approaches [4,5,14]. It is now well established that the pathophysiology of OA extends far beyond the outdated concept of "osteoarthrosis", which implied simple mechanical wear and tear [15]. Instead, OA represents a multifactorial disease involving a complex interplay between low-grade synovial inflammation, subchondral bone remodelling [16,17], meniscal degeneration, and both peripheral and central sensitization of the nervous system [18]. Consequently, reliance on a single therapeutic modality – whether pharmacological, such as oral non-steroidal anti-inflammatory drugs (NSAIDs), or non-pharmacological, such as physical therapy – is often insufficient to address the full spectrum of symptoms or to meaningfully improve quality of life in patients with OA. Major clinical guidelines, including those published by the European

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Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Osteoarthritis Research Society International (OARSI), broadly converge on core management principles, including patient education, structured exercise, and weight management [4,19]. However, discrepancies remain even within these consensus recommendations [4,20]. Such variation reflects the evolving nature of the evidence base and highlights the need for clinicians to translate complex and sometimes inconsistent guidance into coherent, patient-specific treatment strategies. Addressing these challenges requires a multidisciplinary management approach that integrates pharmacological therapy, physical rehabilitation, and psychological support – such as cognitive behavioural strategies – tailored to the individual patient's pain profile, functional deficits, and overall health status.

Stratification and the Promise of Personalized Medicine

The ultimate objective in OA management is the implementation of truly stratified care, in which treatment strategies are tailored the patient's underlying disease phenotype [21,22]. Moving beyond the traditional generic diagnosis of knee OA requires identifying the dominant drivers of disease in individual patients – whether inflammatory, metabolic, or mechanical [9,23,24]. Achieving this precision medicine approach in OA will require the integration of emerging biomarkers and advanced imaging techniques to classify patients into clinically meaningful subgroups [22]. For example, patients present-ing with high levels of synovial inflammation detected through ultrasound or magnetic resonance imaging (MRI) may benefit most from targeted anti-inflammatory therapies or intra-articular interventions before other treatments are considered [25].

Conversely, patients with predominantly mechanical symptoms and minimal inflammatory activity may respond better to biomechanical interventions such as orthotic devices, targeted rehabilitation, or, in selected cases, surgical correction of malalignment. This paradigm shift necessitates clinical assessment tools that extend beyond basic pain scales and subjective questionnaires in order to capture the relative contributions of different disease mechanisms.

The development of simple yet robust digital tools capable of facilitating early phenotyping – potentially through gait analysis or body composition assessment – represents a promising avenue. However, such tools remain largely absent from rou-tine clinical practice. By targeting the specific biological or structural phenotype, stratified management has the potential to improve therapeutic efficacy, reduce ineffective trial-and-error treatment cycles, and optimize healthcare resource utilization.

The Crucial Role of Patient-Centricity and Research Equity

For multimodal and stratified treatment strategies to succeed, they must be firmly grounded in patient-centered care and guided by the principles of research equity. Meeting patient expectations – particularly regarding functional improvement, pain control, and overall quality of life – is essential. Achieving this requires effective multidisciplinary communication, shared decision-making, and a clear understanding of the patient's knowledge of the disease, personal goals, and values. Equally important is the prioritization of diversity and inclusion throughout all stages of clinical research. This includes representation across different patient populations, socioeconomic backgrounds, genetic ancestries, and geographical regions. The exclusion or underrepresentation of specific demographic groups in clinical trials inevitably leads to therapeutic strategies that are effective for some populations but less effective – or even ineffective – for others.

Therefore, a consistent commitment on equity and diversity in research is not merely an ethical obligation but a scientific necessity. Such an approach ensures that identified phenotypes and resulting therapeutic pathways are robust, generalizable, and applicable across the global OA population, ultimately facilitating the implementation of targeted interventions with meaningful worldwide clinical impact.

Conclusion

In conclusion, the future of osteoarthritis management lies in the adoption of stratified, multimodal therapeutic strategies grounded in patient-centered care and research equity. By embracing these principles, the field can move beyond purely symptomatic management and pave the way for meaningful advances in the personalised treatment of osteoarthritis.

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Anatomy, as a fundamental biomedical discipline, plays a crucial role in understanding the structure and function of the human body, as well as in advancing clinical practice and medical education. The continuous development of morphological sciences and their integration with modern diagnostic and research approaches highlight the importance of scientific meetings as platforms for the exchange of knowledge and experience.

In this context, the Serbian Anatomical Society of Serbia is organizing the I**X Congress with international participation**, which will be held from S**eptember 24 to 26, 2026, at the Faculty of Medicine, University of Novi Sad**. The congress will gather leading experts in anatomy from the region and worldwide, aiming to promote the exchange of the latest scientific findings and to strengthen international collaboration in the field of morphological sciences. It is our great pleasure to announce the arrival of Professor Dr. R. Shane Tubbs, a scientist with over 2,000 publications and the Editor-in-Chief of *Gray's Anatomy*.

The scientific program will include plenary lectures, invited lectures, oral and poster presentations, with a particular focus on clinical and applied anatomy, anatomical variations, and contemporary trends in morphological research. Special attention will be dedicated to young researchers, and the best student paper will be awarded and published in the journal *Medicinski pregled*.

Detailed information on the scientific program, abstract submission, and participation is available on the official congress website: **https://www.drustvoanatoma.com/en/congress.html**

Savremena anatomija, kao fundamentalna biomedicinska disciplina, ima ključnu ulogu u razumevanju strukture i funkcije ljudskog organizma, kao i u unapređenju kliničke prakse i medicinskog obrazovanja. Kontinuirani razvoj morfoloških nauka i njihova integracija sa savremenim dijagnostičkim i istraživačkim pristupima ukazuju na značaj naučnih skupova kao prostora za razmenu znanja i iskustava.

*U tom kontekstu, Srpsko anatomsko društvo Srbije organizuje **IX Kongres sa međunarodnim učešćem**, koji će biti održan **na Medicinskom fakultetu Univerziteta u Novom Sadu u periodu od 24. do 26. septembra 2026. godine**. Kongres će okupiti vodeće stručnjake iz oblasti anatomije iz zemlje, regiona i sveta, sa ciljem razmene najnovijih naučnih saznanja i unapređenja međunarodne saradnje u oblasti morfoloških nauka. Posebno nam je zadovoljstvo da najavimo dolazak Profesora dr R. Šejn Tabsa, naučnika sa preko 2000 publikacija i glavnog urednika „Gray's Anatomy".*

Naučni program obuhvatiće plenarna predavanja, predavanja po pozivu, usmene i poster prezentacije, sa posebnim osvrtom na kliničku i primenjenu anatomiju, anatomske varijacije, kao i savremene tokove u morfološkim istraživanjima. Posebna pažnja biće posvećena mladim istraživačima, a najbolji studentski rad biće nagrađen "Jolesovom poveljom" i objavljen u časopisu Medicinski pregled.

Kongres je akreditovan za lekare, stomatologe i stručnjake srodnih biomedicinskih i morfoloških disciplina, sa 13 bodova za predavače po pozivu, 11 bodova za usmenu prezentaciju, 9 bodova za poster prezentaciju i 7 bodova za slušaoce.

*Detaljne informacije o naučnom programu, prijavi radova i registraciji dostupne su na zvaničnoj internet stranici kongresa: **https://www.drustvoanatoma.com/congress.html***

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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

FIFTEEN-YEAR TRENDS IN GROIN WOUND INFECTION AFTER FEMORAL VASCULAR ACCESS – INCIDENCE, SEVERITY, AND MICROBIOLOGICAL SHIFTS IN A TERTIARY CENTER COHORT

PETNAESTOGODIŠNJI TRENDOVI INFEKCIJE PREPONSKE RANE NAKON FEMORALNOG VASKULARNOG PRISTUPA – INCIDENCIJA, TEŽINA I MIKROBIOLOŠKE PROMENE U KOHORTI TERCIJARNOG CENTRA

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Abstract

Introduction. Wound infection after groin incision remains a frequent complication in vascular surgery, yet long-term single-center data on temporal trends, severity distribution, and pathogen shifts are scarce in southeastern Europe. This study describes the 15-year epidemiology of groin wound infection following femoral vascular procedures and examines changes in incidence, wound depth classification, and methicillin-resistant Staphylococcus aureus prevalence. **Material and Methods.** All consecutive groin incisions for femoral arterial access performed at a single tertiary vascular center between January 2010 and December 2024 were reviewed. Wound infection was diagnosed within 90 days using standardized surveillance criteria. Annual rates were calculated and tested for temporal trend. Culture results were analyzed by five-year period. **Results.** Among 8,742 groin incisions, 846 (9.7%) developed a wound infection: 490 superficial (57.9%), 245 deep (29%), and 111 organ/space (13.1%). Annual rates fluctuated between 8.2% and 11.5% without a significant directional trend (p = 0.284). The highest unadjusted rate was observed after infrainguinal bypass (13%). Of 724 culture-positive episodes, the methicillin-resistant Staphylococcus aureus proportion rose across three predefined five-year periods, from 8.7% in 2010–2014 to 13.8% in 2015–2019 and 21% in 2020–2024 (p for trend < 0.001), while gram-negative isolates remained relatively stable at 23–26%. **Conclusion.** Groin wound infection affected approximately one out of ten femoral vascular procedures over 15 years with no measurable decline across the observation period. The steady rise in methicillin-resistant Staphylococcus aureus supports institutional review of empirical prophylaxis protocols at centers with similar resistance profiles.

Key words: Surgical Wound Infection; Groin; Vascular Surgical Procedures; Catheterization; Postoperative Complications; Methicillin-Resistant Staphylococcus aureus; Infections; Risk Factors; Epidemiology; Microbiology

Sažetak

Uvod. Infekcija rane nakon preponske incizije ostaje česta komplikacija vaskularne hirurgije, ali su dugoročni jednocentrični podaci o vremenskim trendovima, distribuciji težine i promenama patogena retki u Jugoistočnoj Evropi. Ova studija opisuje 15-godišnju epidemiologiju infekcije preponske rane nakon femoralnih vaskularnih procedura i ispituje promene u incidenciji, klasifikaciji dubine rane i prevalenciji meticilin-rezistentnog *Staphylococcus*-a *aureus*. **Materijal i metode.** Analizirane su sve uzastopne preponske incizije za femoralni arterijski pristup u jednom tercijarnom vaskularnom centru od januara 2010. do decembra 2024. godine. Infekcija rane je dijagnostikovana u roku od 90 dana korišćenjem standardizovanih kriterijuma nadzora. Godišnje stope su izračunate i testirane na vremenski trend. Rezultati kultura su analizirani po petogodišnjim periodima. **Rezultati.** Od 8.742 preponske incizije, 846 (9,7%) je razvilo infekciju rane: 490 površinskih incizionih (57,9%), 245 dubokih (29%) i 111 organ/prostornih (13,1%). Godišnje stope su varirale od 8,2% do 11,5% bez značajnog trenda (p = 0,284). Najviša neprilagođena stopa je zabeležena nakon infraingvinalnog bajpasa (13%), praćenog aortobifemoralnom rekonstrukcijom (12%). Od 724 kulturom pozitivne epizode, udeo meticilin-rezistentnog *Staphylococcus*-a *aureus* porastao je sa 8,7% u periodu 2010–2014. na 13,8% u periodu 2015–2019. i 21% u periodu 2020–2024. (p za trend < 0,001), dok su Gram-negativni izolati ostali relativno stabilni na 23–26%. **Zaključak.** Infekcija preponske rane zahvatila je približno jednu od deset femoralnih vaskularnih procedura tokom 15 godina bez merljivog smanjenja tokom perioda posmatranja. Stalni porast meticilin-rezistentnog *Staphylococcus*-a *aureus* podržava institucionalno preispitivanje protokola empirijske profilakse u ustanovama sa sličnim profilom rezistencije.

Ključne reči: infekcija hirurške rane; prepone; vaskularne hirurške procedure; kateterizacija; postoperativne komplikacije; meticilin-rezistentni Staphylococcus aureus; infekcija; faktori rizika; epidemiologija; mikrobiologija

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Abbreviations

SSI – surgical site infection
MRSA – methicillin-resistant Staphylococcus aureus
MSSA – methicillin-susceptible Staphylococcus aureus
EVAR – endovascular aneurysm repair
GIVE – Groin wound Infection after Vascular Exposure
NSQIP – National Surgical Quality Improvement Program
EUCAST – European Committee on Antimicrobial Susceptibility Testing

Introduction

Groin incision remains a common access route in open and hybrid vascular procedures and continues to be associated with clinically important postoperative wound morbidity [1–4]. Published incidence figures range widely, from below 3% in endovascular series to over 40% in high-risk bypass cohorts, reflecting heterogeneity in case selection, follow-up duration, and diagnostic criteria [3,5].

Local surveillance data may help contextualize institutional wound infection burden, identify procedure groups with higher wound morbidity, and monitor microbiological shifts over time. However, most existing reports originate from multicenter registries with short recruitment windows or from Western European and North American settings [1,2,6]. We identified limited published long-term single-center surveillance data from southeastern European vascular centers, despite regional antimicrobial resistance profiles that may diverge from Western European benchmarks [7,8].

This study had three objectives: first, to characterize the 15-year incidence and severity distribution of groin wound infection after femoral vascular access at a tertiary referral center; second, to examine whether infection rates changed over time; and third, to describe the microbiological spectrum with particular attention to methicillin-resistant Staphylococcus aureus (MRSA) trends.

Material and Methods

Study design and setting

A retrospective observational study was conducted at the sole tertiary vascular unit serving a geographically defined catchment of approximately two million inhabitants. The review covered all consecutive femoral-access vascular procedures performed between January 1, 2010 and December 31, 2024. Clinical, operative, and microbiological records were linked through the institutional hospital information system. Approval was obtained from the Institutional Ethics Committee (Protocol 01-19-103-2/24); individual consent was waived given the retrospective, non-interventional design.

Study population

A total of 12,180 groin and lower-extremity vascular procedures were identified in the operative database. After excluding 2,156 purely percutaneous approaches that did not require a skin incision and a further 1,282 cases with pre-existing wound infection (n = 187), non-femoral arterial access (n = 892), or documentation insufficient for outcome determination (n = 203), the analysis comprised 8,742 evaluable groin incisions in 7,218 individual patients.

Outcome definition

Groin wound infection was classified according to the surveillance definitions of the United States Centers for Disease Control and Prevention: superficial incisional (involving skin and subcutaneous tissue), deep incisional (fascia and muscle), and organ/space (vascular graft or perigraft tissue) [9]. A uniform 90-day surveillance window was applied to all procedures because the majority involved prosthetic material, for which extended follow-up is mandated, and because deep infections characteristically present two to four weeks after the index operation [4,10]. Two vascular surgeons independently adjudicated every case without access to each other's assessment; a third surgeon arbitrated the small proportion of disagreements (4.2%).

Microbiological data

Wound cultures were obtained at the discretion of the treating surgeon whenever clinical infection was suspected. Specimens were processed using standard aerobic and anaerobic protocols. Antibiotic susceptibility was determined by disc diffusion and automated systems according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [11]. MRSA was defined phenotypically by cefoxitin resistance confirmed by molecular testing when available.

Statistical analysis

Categorical variables are expressed as absolute counts and percentages; continuous variables as means with standard deviation or medians with interquartile range where appropriate. Patient-level characteristics (age, sex, diabetes, obesity, chronic kidney disease, smoking, immunosuppression) are reported per individual patient, whereas operative characteristics (procedure type, anesthesia, prosthetic material) are reported per groin incision. Annual infection rates were calculated as the number of events divided by the number of incisions performed in that calendar year, with Wilson 95% confidence intervals. Temporal trends were evaluated with the Cochran–Armitage test for proportions. As a sensitivity analysis, temporal change in infection incidence was additionally modeled using

binomial regression with calendar year as an ordinal predictor, reporting the estimated annual change and 95% confidence interval. Changes in pathogen distribution across three predefined five-year strata (2010–2014, 2015–2019, 2020–2024) were compared using χ^2 tests. Procedure-specific and severity subgroup comparisons were descriptive and exploratory; p values from these analyses should be interpreted cautiously. No a priori sample size calculation was performed because the study included all consecutive eligible procedures during the predefined 15-year period. Because a uniform 90-day surveillance window was applied to all procedures regardless of implant status, the reported incidence for non-prosthetic procedures (endarterectomy, groin cutdown) may be higher than in series using a 30-day definition. Direct comparisons with studies applying shorter surveillance windows should therefore be interpreted with caution. Multivariable risk-factor analysis was not performed because the primary aim was descriptive trend characterization; a companion prediction model study from the same cohort has been reported separately (Nikolić et al., submitted). This study is reported in accordance with the STROBE statement for observational cohort studies. Statistical significance was set at a two-sided $p < 0.05$. Analyses were performed in R version 4.3.2.

Results

Patient and procedural characteristics

The 8,742 groin incisions were performed in 7,218 patients with a mean age of 67.4 ± 10.8 years; 65% were men. The most prevalent comorbidities were diabetes mellitus (36%), active smoking (41%), obesity (27%), and chronic kidney disease (21%). Infrainguinal bypass accounted for 32.4% of incisions, followed by femoral endarterectomy (21.6%), aortobifemoral reconstruction (17%), endovascular repair with groin cutdown (15.4%), and other femoral-access procedures (13.6%) **(Table 1).**

Overall incidence and severity

Wound infection was identified in 846 of 8,742 incisions, yielding an overall rate of 9.7% (95% confidence interval 9.1–10.3). Superficial infections constituted the largest category (490 episodes; 57.9%), followed by deep incisional infections (245; 29%) and organ/space involvement (111; 13.1%). The median time from operation to diagnosis was 12 days (interquartile range 7–21) for superficial infections, 19 days (12–32) for deep infections, and 26 days (16–48) for organ/space infections.

Incidence by procedure type

Procedure-specific rates showed substantial variation **(Table 2).** The highest unadjusted infection rate was observed after infrainguinal bypass at 13% (95% confidence interval 11.8–14.3), with a notable proportion of deep and organ/space infections (41%). Aortobifemoral procedures followed at 12% (10.4–13.7). Femoral endarterectomy and endovascular groin cutdown had lower rates of 7.5% and 5.5%, respectively. These procedure-specific differences should be interpreted as unadjusted surveillance findings and not as independent estimates of procedural risk, because bypass patients typically carry a heavier comorbidity burden. The "other femoral access" category, which

Table 1. Baseline characteristics

Characteristic	n or mean	
Total groin incisions	8,742	100
Individual patients	7,218	–
Age, years, mean ± SD	67.4	±10.8
Male sex	4,692	65.0
Diabetes mellitus	2,598	36.0
Active smoking	2,959	41.0
Obesity (body mass index ≥30)	1,949	27.0
Chronic kidney disease	1,516	21.0
Immunosuppressive therapy	505	7.0
Infrainguinal bypass	2,834	32.4
Femoral endarterectomy	1,892	21.6
Aortobifemoral reconstruction	1,486	17.0
EVAR with groin cutdown	1,342	15.4
Other femoral-access procedures	1,188	13.6
General anesthesia	6,367	72.8
Prosthetic material implanted	5,981	68.4

EVAR – endovascular aneurysm repair. Patient-level characteristics (age, sex, comorbidities) are reported per individual patient (n = 7,218); operative characteristics (procedure type, anesthesia, prosthetic material) are reported per groin incision (n = 8,742).

Table 2. Infection rates by procedure and severity

Procedure	n	SSI, n (%)	Superficial incisional	Deep	Organ/space (graft)	
Infrainguinal bypass	2,834	369 (13.0)	216	107	46	11.8–14.3
Aortobifemoral	1,486	178 (12.0)	94	56	28	10.4–13.7
Femoral endarterectomy	1,892	142 (7.5)	90	38	14	6.4–8.8
EVAR cutdown	1,342	74 (5.5)	46	20	8	4.4–6.9
Other femoral access	1,188	83 (7.0)	44	24	15	5.7–8.6
Total	8,742	846 (9.7)	490	245	111	9.1–10.3

95% CI: Wilson method; SSI – surgical site infection

encompassed thrombectomy, embolectomy, and re-operative femoral exposure, accounted for 18.1% organ/space infections, possibly reflecting heterogeneous indications and re-operative tissue disruption.

Temporal trends in overall and severity-specific rates

Annual infection rates ranged from a low of 8.2% in 2014 to a peak of 11.5% in 2017 **(Table 3, Graph 1)**. The Cochran–Armitage test detected no significant directional change over the 15-year observation period ($p = 0.284$). Binomial regression with calendar year as an ordinal predictor estimated an annual change in infection rate of +0.02 percentage points (95% confidence interval −0.12 to +0.16), consistent with the non-significant trend test. When examined by severity category, superficial infections remained the predominant subtype throughout, and the proportion of organ/space infections varied between 10.6% and 13.3% across the three five-year periods (13% in 2010–2014, 10.6% in 2015–2019, and 13.3% in 2020–2024; $p = 0.58$) without a consistent directional trend. The COVID-19 pandemic years (2020–2021) were associated with a transient dip in operative volume but no detectable change in infection rates, consistent with findings from Italian vascular centers [7].

Microbiological spectrum and MRSA trends

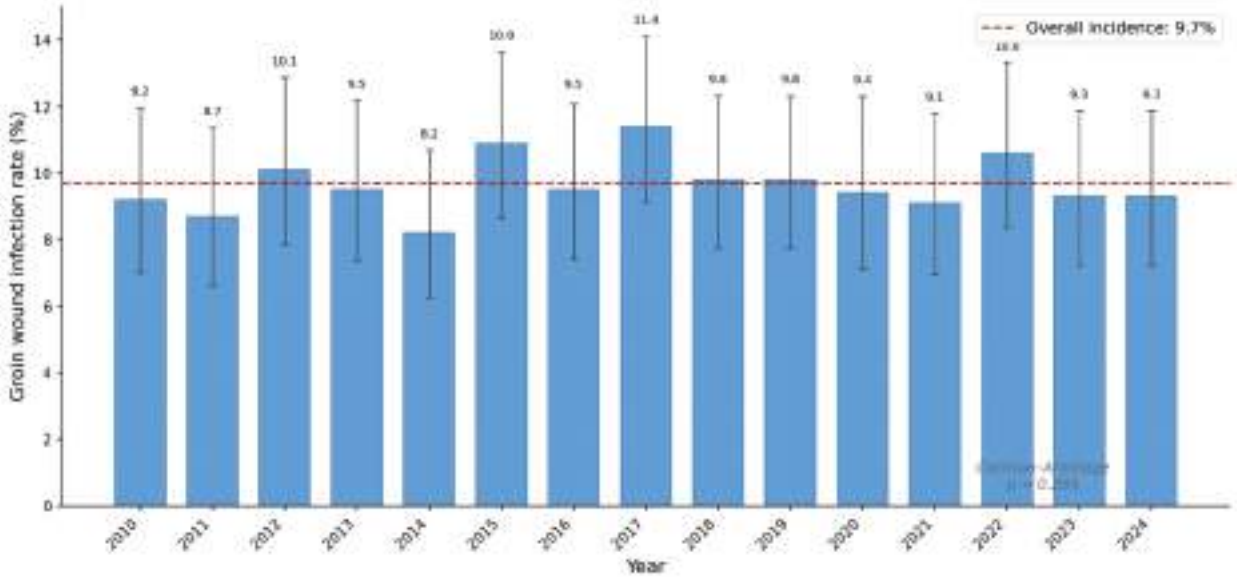
Culture results were available for 724 of 846 infection episodes (85.6%): 219 of 253 (86.6%) in 2010–2014, 276 of 322 (85.7%) in 2015–2019, and 229 of 271 (84.5%) in 2020–2024, indicating stable sampling practice across periods. Staphylococcus aureus was the single most common isolate, identified in 319 episodes (44.1% of culture-positive cases). Coagulase-negative staphylococci accounted for 98 (13.5%), Escherichia coli and other Enterobacterales for 131 (18.1%), Pseudomonas aeruginosa for 47 (6.5%), enterococci for 52 (7.2%), anaerobes for 29 (4%), and polymicrobial growth was recorded in 48 (6.6%) **(Table 4).**

The proportion of MRSA among all S. aureus isolates rose steadily across the three five-year periods: 19 of 88 (21.6%) in 2010–2014, 38 of 122 (31.1%) in 2015–

Table 3. Annual infection rates

Year	Incisions	SSI, n	Rate %	Superficial incisional	Deep	Organ/space (graft)
2010	524	48	9.2	28	13	7
2011	538	47	8.7	26	15	6
2012	556	56	10.1	32	16	8
2013	568	54	9.5	30	17	7
2014	584	48	8.2	29	14	5
2015	598	65	10.9	37	19	9
2016	612	58	9.5	35	16	7
2017	628	72	11.4	42	21	9
2018	642	63	9.8	37	17	9
2019	656	64	9.8	38	18	8
2020	488	46	9.4	26	14	6
2021	548	50	9.1	27	15	8
2022	592	63	10.6	37	18	8
2023	604	56	9.3	34	14	8
2024	604	56	9.3	32	18	6
Total	8,742	846	9.7	490	245	111

Cochran–Armitage trend test $p = 0.284$.



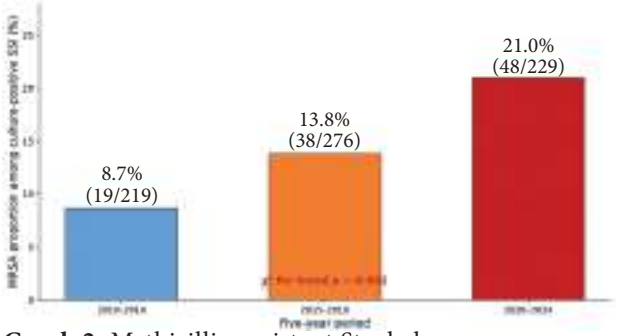
Graph 1. Annual groin wound infection rate (%), 2010–2024. Error bars: Wilson 95% confidence intervals. Dashed line: overall 15-year incidence (9.7%). Cochran–Armitage trend test p = 0.284.

Table 4. Microbiological spectrum by five-year period

Organism	2010–2014	2015–2019	2020–2024	
S. aureus (MSSA)	69 (31.5)	84 (30.4)	61 (26.6)	214 (29.6)
S. aureus (MRSA)	19 (8.7)	38 (13.8)	48 (21.0)	105 (14.5)
Coagulase-neg. staph.	32 (14.6)	37 (13.4)	29 (12.7)	98 (13.5)
Escherichia coli	30 (13.7)	36 (13.0)	28 (12.2)	94 (13.0)
Other Enterobacterales	12 (5.5)	14 (5.1)	11 (4.8)	37 (5.1)
Pseudomonas aeruginosa	15 (6.8)	18 (6.5)	14 (6.1)	47 (6.5)
Enterococcus spp.	17 (7.8)	20 (7.2)	15 (6.6)	52 (7.2)
Anaerobes	9 (4.1)	11 (4.0)	9 (3.9)	29 (4.0)
Polymicrobial	16 (7.3)	18 (6.5)	14 (6.1)	48 (6.6)
Culture-positive total	219	276	229	724*
Culture-negative	34	46	42	122

Denominators are culture-positive episodes per period (2010–2014: 219; 2015–2019: 276; 2020–2024: 229; total: 724). Values are n (% of culture-positive episodes in that period). MSSA = methicillin-susceptible S. aureus; MRSA = methicillin-resistant S. aureus. *724/846 = 85.6% culture positivity. χ^2 for MRSA trend across periods: p < 0.001.

2019, and 48 of 109 (44%) in 2020–2024 (χ^2 for trend p < 0.001). When expressed as a fraction of all culture-positive episodes regardless of organism, MRSA increased from 8.7% (2010–2014) to 13.8% (2015–2019) to 21% (2020–2024) across the same intervals **(Graph 2).** In a crude logistic regression model with five-year period coded as an ordinal variable (1, 2, 3) and culture-positive methicillin-resistant Staphylococcus aureus as the outcome, the odds ratio per period was 1.56 (95% confidence interval 1.28–1.91; denominator: all 724 culture-positive episodes). Gram-negative organisms remained relatively stable at approximately 23–26% of culture-positive episodes throughout the study period. No vancomycin-resistant enterococci were detected.



Graph 2. Methicillin-resistant Staphylococcus aureus as a proportion of all culture-positive groin wound infections across three five-year periods (2010–2014, 2015–2019, 2020–2024). χ^2 for trend p < 0.001.

Discussion

In this 15-year cohort of nearly nine thousand femoral-access groin incisions at a single vascular center in southeastern Europe, the two clinically most relevant findings were the stable overall wound infection incidence of 9.7% and the increasing methicillin-resistant Staphylococcus aureus proportion among culture-positive infections. Additionally, infection severity was not uniform across procedure types, with bypass operations accounting for a disproportionate share of deep and organ/space infections.

The overall rate of 9.7% aligns with the 8.6% reported by the multicenter Groin wound Infection after Vascular Exposure (GIVE) cohort from 37 centers in the United Kingdom [1], and falls within the 5–15% range cited in recent systematic reviews [3,5]. No decline in wound infection incidence was observed across the study period. Similar stable rates have been described in contemporary vascular surgery series, although direct comparison is limited by differences in surveillance definitions and case mix [6,12]. One possible explanation is that increasing patient complexity may have offset improvements in perioperative technique and infection-prevention practice, as rising prevalence of diabetes, obesity, and immunosuppressive therapy – offsets improvements in technique and infection-prevention bundles.

The unadjusted procedure-specific gradient observed here – highest after infrainguinal bypass (13%), intermediate after aortobifemoral reconstruction (12%), and lowest after endovascular groin cutdown (5.5%) – mirrors the pattern described by Jim and colleagues using the NSQIP database [13]. The higher rates after bypass procedures likely reflect a combination of operative complexity, prosthetic use, and underlying patient risk profile rather than an independent procedural effect. The relatively high organ/space proportion after bypass operations (12.5%) underscores the vulnerability of prosthetic conduits to late haematogenous and contiguous seeding.

Methicillin-resistant Staphylococcus aureus accounted for 8.7% of culture-positive infections in 2010–2014 and 21% in 2020–2024, indicating a marked increase over time. Between the first and last five-year periods, the MRSA share among staphylococcal isolates approximately doubled, from 22% to 44%. This trend echoes surveillance data from vascular units in Italy and Germany [7,8] and has practical consequences: standard cephalosporin-based prophylaxis may offer inadequate coverage for a growing subset of patients. Several guidelines suggest that MRSA-active prophylaxis may be considered when local MRSA prevalence among SSI pathogens is high, particularly in the context of prosthetic implantation [10,14]. At our institution, the observed MRSA proportions now fall within a range in which some guidelines consider augmented prophylactic coverage, although any policy change should be based on local stewardship review [15].

Gram-negative organisms, predominantly Escherichia coli and Pseudomonas aeruginosa, remained relatively stable at approximately 23–26% of culture-positive episodes throughout the study period. The stable gram-negative proportion should be interpreted alongside emerging reports of extended-spectrum β-lactamase producers in vascular wound infections at other centers [7], which warrants continued local antibiogram monitoring.

The study includes all eligible procedures performed at the institution during the 15-year period, which strengthens internal completeness of surveillance data and supports genuine trend analysis; however, referral-related case mix may still limit external generalizability. Blinded dual-surgeon adjudication and a standardized 90-day follow-up window reduce both ascertainment bias and under-reporting. The main limitations are as follows. First, the single-center design restricts generalizability; the observed MRSA trajectory should be interpreted primarily as an institutional surveillance signal and should not be extrapolated directly to centers with different case-mix, microbiological ecology, or prophylaxis protocols. Second, the retrospective nature precluded collection of certain variables such as nasal MRSA carriage status, details of skin preparation, and compliance with prophylaxis timing. Third, wound cultures were obtained at the treating surgeon's discretion rather than by standardized protocol; microbiological trend analyses were therefore restricted to culture-positive infections and may have been influenced by temporal variation in sampling practices, which could not be fully reconstructed retrospectively. Fourth, 1,282 procedures were excluded, including 203 with insufficient documentation; a comparison of included and excluded cases was not possible because the excluded group lacked the outcome data needed for meaningful comparison. Fifth, missing baseline data (such as body mass index in patients without recent measurement) were not systematically quantified; however, the core variables used in trend analysis were complete for all included cases. Sixth, because 8,742 incisions arose from 7,218 patients (21.1% contributing more than one incision), within-patient correlation was not modeled in the trend analysis; confidence intervals and p-values may therefore be modestly underestimated. A cluster-corrected model (e.g. generalized estimating equations with patient-level clustering) would be desirable but was beyond the scope of this descriptive report. Finally, culture-negative infections (14.4%)

may include both true infections with fastidious organisms and cases treated empirically before sampling, potentially underestimating the MRSA burden.

Conclusion

Over a 15-year period, approximately one in ten groin incisions for femoral vascular access developed a wound infection, with no measurable decline across the observation period. Bypass procedures had the highest unadjusted infection rates and the greatest proportion of deep and graft-level infections. The steady and substantial rise in methicillin-resistant Staphylococcus aureus prevalence –from approximately 9% to 21% of culture-positive episodes – supports institutional review of prophylaxis and antimicrobial stewardship policies, particularly where similar resistance patterns are confirmed in the local antibiogram. Prospective surveillance incorporating nasal screening and prophylaxis-outcome linkage would help determine whether targeted methicillin-resistant Staphylococcus aureus decolonisation or augmented antibiotic regimens can reduce this persistent complication.

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PAIN ASSESSMENT FOLLOWING GASTROINTESTINAL ENDOSCOPIC PROCEDURES IN THE PEDIATRIC POPULATION – A PROSPECTIVE OBSERVATIONAL STUDY

PROCENA BOLA NAKON GASTROINTESTINALNIH ENDOSKOPSKIH PROCEDURA U PEDIJATRIJSKOJ POPULACIJI – PROSPEKTIVNA OPSERVACIONA STUDIJA

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Abstract

Introduction. Gastrointestinal endoscopic procedures are increasingly performed in pediatric populations; however, data on postprocedural pain and its determinants remain limited. Adequate sedation and effective pain management are essential for ensuring patient comfort and optimizing procedural outcomes. This study is aimed to evaluate intensity of postprocedural pain following gastrointestinal endoscopic procedures in children and to identify factors associated with increased pain perception. **Material and Methods.** This prospective clinical study included pediatric patients undergoing elective endoscopic procedures at the Pediatric Clinic in Novi Sad between May and July 2025. Pain intensity was assesses 30 minutes after the procedure using age-appropriate validated scales: the Numerical Rating Scale for children aged ≥9 years, the Wong-Baker Faces Pain Rating Scale, and the Face, Legs, Activity, Cry, Consolability scale for younger children. Patient demographics, procedural characteristics (type and duration), and overall satisfaction were analyzed. Statistical analysis was performed using SPSS version 23. **Results.** A total of 39 patients were included (16 boys and 23 girls). The most frequently performed procedure was combined esophagogastroduodenoscopy and colonoscopy (61.5%). The mean pain score was 2.69 (SD = 1.73), ranging from 0 to 6. Female patients reported higher pain scores (mean = 3.08) compared to males (mean = 2.12), with the difference approaching statistical significance (p = 0.086). No statistically significant associations were observed between pain intensity and age, type or duration of the procedure, or prior endoscopic experience. The mean satisfaction score was 4.64 (SD = 0.58), with significantly higher satisfaction reported among younger patients (p = 0.03). **Conclusion.** Identification of individual risk factors for postprocedural pain may facilitate optimization of sedation protocols and support more patient-centered approach in pediatric endoscopy.

Key words: Pain; Pain Measurement; Endoscopy, Gastrointestinal; Pediatrics; Child; Adolescent; Postoperative Pain; Pain Management; Analgesia; Risk Factors

Sažetak

Uvod. Gastrointestinalne endoskopske procedure mogu biti povezane sa nelagodnošću, bolom, anksioznošću, naročito u pedijatrijskoj populaciji. Cilj ovog istraživanja bio je procena intenziteta bola nakon gastroenterološkihendoskopskih procedura u pedijatrijskom uzrastu, kao i ispitivanje potencijalnih faktora rizika za veći stepen bola nakon pregleda. **Materijal i metode.** Istraživanje je sprovedeno kao klinička prospektivna studija. U analizu su uključeni pacijenti podvrgnuti elektivnim endoskopskim procedurama na Klinici za pedijatriju u Novom Sadu u periodu od maja do jula 2025. godine. Uvidom u medicinsku dokumentaciju analizirani su: osnovni podaci o pacijentima, dijagnoza, vrsta i trajanje endoskopske procedure. Za evaluaciju bola nakon endoskopskih procedura korišćene su numerička skala bola, Vong–Bejkerova skala (*Wong-Baker*) za procenu bola i skala *Face, Legs, Activity, Cry, Consolability*. **Rezultati.** U istraživanju je učestvovalo 39 pacijenata, od toga 16 dečaka i 23 devojčice. Najčešće je sprovođena kombinacija ezofagogastroduodenoskopije i kolonoskopije u istom aktu, kod 24 pacijenta (61,5%). Minimalna ocena bola za ukupan uzorak bila je 0, a najviša 6, sa prosečnom vrednosti od 2,69, i standardnom devijacijom od 1,73. Što se pola tiče, registrovana je marginalna statistička razlika između dečaka i devojčica – p = 0,086, u korist izraženije percepcije bola kod devojčica (M = 3,08, SD = 1,62) nasuprot dečaka (M = 2,12, SD = 1,72). **Zaključak.** Adekvatna sedacija i analgezija omogućava veći broj uspešnih pregleda i obezbeđuje bolje iskustvo pacijentima koji se podvrgavaju endoskopskim procedurama. Poznavanje faktora rizika za veći stepen postproceduralnog bola može doprineti poboljšanju ovih strategija i formiranje individualnog pristupa za svakog pacijenta.

Ključne reči: bol; procena bola; endoskopija gastrointestinalnog trakta; pedijatrija; dete; adolescent; postoperativni bol; upravljanje bolom; analgezija; faktori rizika

Introduction

Gastrointestinal endoscopy has undergone significant evolution over the past century, progressing from rigid instruments to flexible fiberoptic and advanced video-assisted systems. These technological advancements, along with improvements in sedation techniques, have significantly expanded the applicability of endoscopy in pediatric populations. Currently, gastrointestinal endoscopic procedures are

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Abbreviations

ASA	– The American Society of Anesthesiologists
EGD	– esophagogastroduodenoscopy
FLACC Scale	– Face, Legs, Activity, Cry, Consolability Scale
FACES	– Wong-Baker FACES Pain Rating Scale
NRS	– Numerical Rating Scale

routinely performed in children for both diagnostic and therapeutic purposes [1].

Despite its clinical utility, endoscopy remains an inherently invasive procedure and may be associated with discomfort, pain, anxiety, and procedural stress, particularly in pediatric patients. In developed healthcare settings, most routine pediatric endoscopic procedures are performed under some form of sedation or general anesthesia [2]. Adequate sedation facilitates a more comprehensive examination, enhances patient cooperation, and contributes to overall procedural success. Furthermore, it has been shown to increase acceptance of repeat procedures among both patients and their caregivers when clinically indicated [3,4].

The American Society of Anesthesiologists (ASA) classifies sedation into a continuum ranging from minimal sedation to general anesthesia. In pediatric practice, European guidelines recommend that endoscopic procedures be performed under general anesthesia whenever feasible, with deep sedation considered an acceptable alternative when general anesthesia is not available [5,6]. Sedation strategies vary widely, ranging from moderate sedation using benzodiazepines and opioids to deep sedation with agents such as propofol, often administered in combination with analgesics to achieve synergistic effects [7,8].

Although sedation improves procedural tolerance, gastrointestinal endoscopy may still be followed by postprocedural discomfort or pain. Data on post-endoscopic pain in pediatric population remain limited, particularly regarding factors that may influence pain perception. Previous studies have suggested that female sex, prolonged procedure duration, and certain gastrointestinal conditions – such as irritable bowel syndrome – may be associated with increased pain perception [9]. Identification of such factors is essential for optimizing sedation and analgesia protocols and for enhancing the overall patient experience in pediatric endoscopy.

The aim of this study was to evaluate intensity of postprocedural pain following gastrointestinal endoscopic procedures in children and to identify factors associated with increased pain perception.

Material and Methods

This prospective observational clinical study was conducted at the Pediatric Clinic in Novi Sad between May and July 2025. The study population comprised pediatric patients undergoing elective gastrointestinal endoscopic procedures. Two patients with significant neurological impairments were excluded due to the inability to reliably assess pain.

Patient data were collected from medical records and included demographic characteristics, clinical diagnosis, type of endoscopic procedure, and procedure duration. Postprocedural pain intensity was assessed 30 minutes after completion of the procedure using age-appropriate, validated assessment tools:

– Numerical Rating Scale (NRS) (0 = no pain, 5 = moderate pain, 10 = worst imaginable pain), used for children aged ≥ 9 years [10] (**Figure 1**);

– Wong-Baker FACES Pain Rating Scale (FACES) (0–10 scale), used for children aged 0–8 years, based on facial expression [10] (**Figure 1**);

– FLACC Scale (Face, Legs, Activity, Cry, Consolability), used for children aged 0–8 years, based on behavioral observation [11].

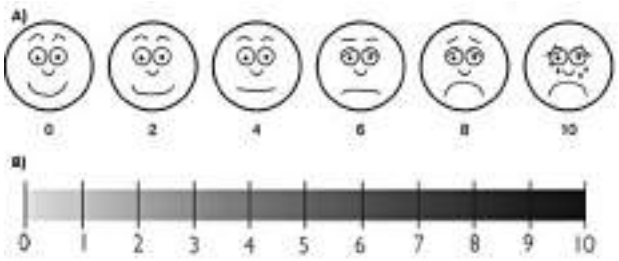

Figure 1. A) FACES Pain Rating Scale; B) Numerical Rating Scale

Table 1. FLACC Pain Assessment Scale

Category	Score 0	Score 1	Score 2
Face	No expression or smile	Occasional grimace or frown, with drawn	Frequent to constant frown, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless	Kicking or legs drawn up
Activity	Lying quietly, normal movement	Squirming, shifting back and forth	Arched, rigid or jerking
Cry	No crying	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs
Consolability	Content, relaxed	Reassured by touching, hugging	Difficult to console or comfort

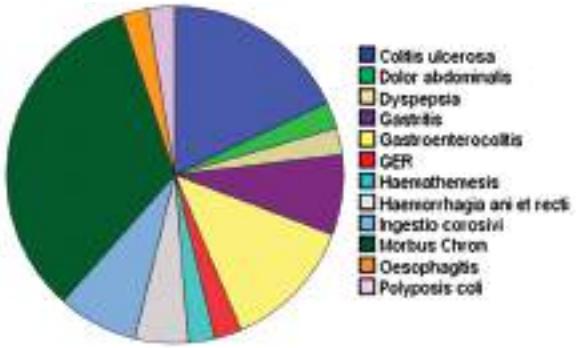

Figure 2. Diagnostic distribution among patients

The FLACC scale employs a three-point scoring system across five behavioral domains, with higher cumulative scores indicating greater pain intensity (**Table 1**).

In addition to pain assessment, caregiver-reported overall satisfaction with the procedure was recorded using a five-point Likert scale (1 = extremely dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, 5 = extremely satisfied).

All data were entered into a structured database and analyzed using IBM SPSS Statistics, version 23. Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages. Between-group comparisons were performed using the independent samples *t*-test, analysis of variance (ANOVA), and Pearson's correlation coefficient, as appropriate. A *p*-value of < 0.05 was considered statistically significant.

The study protocol was approved by the Ethics Committee of the Institute for Health Care of Children and Youth of Vojvodina. Written informed consent was obtained from the parents or legal guardians of all participants prior to study inclusion.

Results

Patient Characteristics

A total of 39 pediatric patients were included in the study, comprising 16 males and 23 females. The age of participants ranged from 1 to 18 years, with a mean age of 12.28 ± 4.71 years. The mean body weight was 47.66 ± 19.68 kg (range: 10–86 kg). Twelve distinct diagnostic categories were identified, with Crohn's disease and ulcerative colitis representing the most prevalent conditions. The distribution of diagnoses is presented in **Figure 2**.

Procedural Characteristics

The most frequently performed procedure was combined esophagogastroduodenoscopy (EGD) and colonoscopy during a single session, conducted in 24 patients (61.5%). Isolated EGD was performed in 9 patients (23.1%), while isolated colonoscopy was performed in 6 patients (15.4%). For 21 patients (53.8%), this was their first endoscopic procedure. The mean procedure duration was 32.05 ± 11.56 minutes, ranging from 10 to 50 minutes. The distribution of procedure duration is illustrated in **Figure 3**.

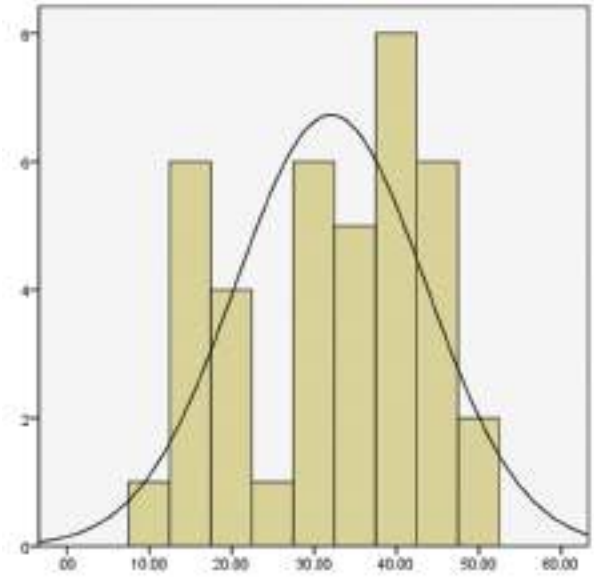

Figure 3. Distribution of procedure duration (in minutes)

Postprocedural Pain and Satisfaction

Postprocedural pain intensity constituted the primary outcome of the study. The **mean pain score** was **2.69 ± 1.73**, with values ranging from 0 to 6. The distribution of pain scores is shown in **Figure 4.**

Overall satisfaction with the procedure was high, with a mean score of 4.64 ± 0.58 (ranging: 3-5), as presented in **Figure 5**.

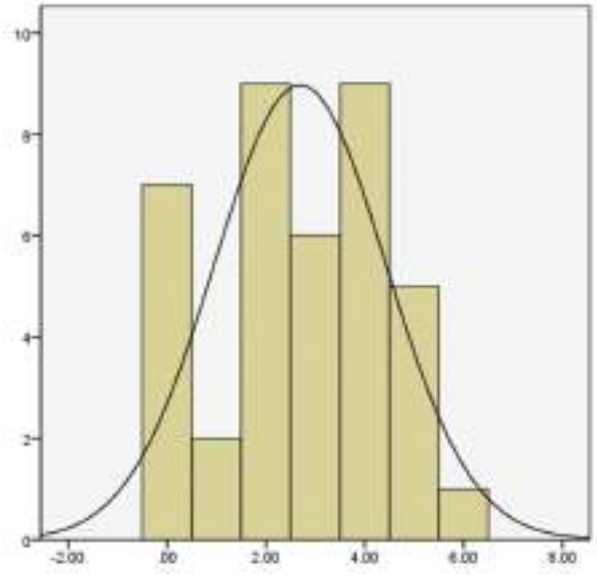

Figure 4. Distribution of reported pain scores

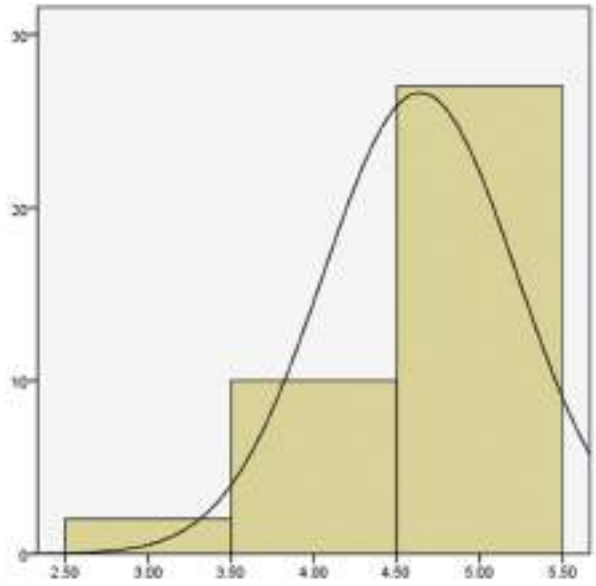

Figure 5. Distribution of overall satisfaction scores

Sex-Based and Procedure-Based Comparisons

A difference in pain perception between sexes approached statistical significance. **Female patients** reported higher mean pain scores (**3.08 ± 1.62**) compared to **males** (**2.12 ± 1.72**) (*t(37) = -1.749, p = 0.086).*

No statistically significant differences in pain intensity were observed between patients undergoing their first endoscopic procedure and those with prior experience (*t(37) = 0.45, p = 0.65*), nor across different types of procedures (*F(2) = 1.2, p = 0.28).*

Correlation analyses revealed no significant associations between pain scores and body weight (*r = -0.18, p = 0.28)*, procedure duration (*r = 0.07, p = 0.65)* or overall satisfaction (*r = 0.008, p = 0.95).*

Satisfaction Analysis

No significant differences in satisfaction scores were identified between sexes (*t(37) = -0.14, p = 0.90),* nor between patients with and without prior endoscopic experience (*t(37) = 1.41, p = 0.16).* However, age demonstrated a statistically significant negative correlation with satisfaction (*r = -0.34, p = 0.03*) indicating that younger patients reported higher levels of satisfaction.

Discussion

This study evaluated postprocedural pain in children undergoing elective gastrointestinal endoscopic procedures and explored factors potentially associated with increased pain perception. Effective pain management represents a cornerstone of pediatric care, not only by ensuring immediate patient comfort but also by reducing anxiety, facilitating recovery, and improving the overall healthcare experience.

Pain is an inherently subjective and multifactorial phenomenon. Its assessment in pediatric populations is particularly challenging due to variability in cognitive development and communication abilities [10]. Consequently, the use of age-appropriate, validated assessment tools is essential. In older children, self-report instruments such as numerical rating scales are considered the gold standard, whereas in younger or nonverbal children, observational tools such as the FLACC and Wong-Baker FACES scales are widely utilized. Although these instruments are clinically practical, they rely on observer interpretation and are therefore subject to inherent limitations. Nevertheless, behavioral indicators – including facial expression, crying, motor activity, and consolability – remain indispensable components of pediatric pain assessment [11–13].

In the present study, the mean postprocedural pain score was relatively low (2.69), with a maximum value of 6, indicating that the procedures were generally well tolerated. A trend toward higher pain scores was observed in female patients compared to males. Although this difference did not reach statistical significance, it is consistent with previous reports suggesting greater pain sensitivity and reporting among female pediatric patients [9]. However, pain perception is influenced by a complex interplay of biological, physiological, and sociocultural factors, and these sex-related differences warrant further investigation in larger, adequately powered studies.

No statistically significant associations were identified between pain intensity and procedural characteristics. These findings differ from some reports in the literature that link longer or more invasive procedures with increased postprocedural pain [14]. The lack of significant associations in our study may be attributable to the relatively small sample size and the predominance of combined upper and lower endoscopy, which limited variability across procedural categories.

Psychological factors, particularly anxiety and fear, play a critical role in modulating pain perception in pediatric patients. Preprocedural anxiety has been consistently associated with increased postprocedural discomfort [15]. In our cohort, patients undergoing endoscopy for the first time tended to report higher pain scores, although this trend did not achieve statistical significance. This observation supports the hypothesis that unfamiliarity with medical procedures may amplify stress responses and perceived pain [16]. These findings highlight the importance of implementing child-centered communication strategies and preparatory interventions aimed at reducing anxiety prior to the procedure.

Overall satisfaction with the endoscopic experience was high among both participants and their caregivers. Notably, a significant inverse correlation was observed

between age and satisfaction, with younger patients reporting higher satisfaction levels. This finding may reflect lower anticipatory anxiety, fewer prior negative healthcare experiences, or a greater reliance on caregiver support in younger children. High satisfaction rates are particularly relevant in pediatric patients with chronic gastrointestinal disorders, who often require repeated endoscopic evaluations throughout their clinical course.

Several limitations of this study should be acknowledged. First, the relatively small sample size and single-center design limit the generalizability of the findings. Second, pain assessment was conducted at a single time point – 30 minutes post-procedure – without longitudinal follow-up. A more comprehensive evaluation, including serial pain assessment and documentation of analgesic requirements, would provide a more nuanced understanding of postprocedural pain dynamics. Finally, preprocedural anxiety was not formally assessed, which may have further elucidated individual differences in pain perception.

Despite these limitations, this study contributes to the growing body of evidence in pediatric endoscopy and underscores the importance of individualized sedation and analgesia strategies. Future research should incorporate larger, multicenter cohorts, longitudinal pain assessments, and psychological profiling to better characterize and mitigate postprocedural discomfort in pediatric populations.

Conclusion

Effective sedation and analgesia are essential for the safe and successful performance of gastrointestinal endoscopic procedures in pediatric patients. Although most children tolerate these procedures well, certain subgroups may be at increased risk for experiencing greater postprocedural pain. In the present study, overall pain intensity was low and patient satisfaction was high. However, observed trends toward higher pain perception in female patients and in those undergoing endoscopy for the first time suggest that individual patient characteristics and prior experience may influence outcomes.

Identification of these risk factors may assist clinicians in anticipating patient needs, optimizing perioperative care, and implementing individualized strategies to minimize discomfort and enhance the overall endoscopic experience. Further, large-scale, multicenter studies with extended follow-up are warranted to validate these findings and refine sedation protocols in pediatric endoscopy.

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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

OUTCOMES AND COMPLICATIONS OF OPEN SURGICAL CAROTID ARTERY REVASCULARIZATION IN RELATION TO CLINICAL PRESENTATION OF THE DISEASE

ISHODI I KOMPLIKACIJE OTVORENE HIRURŠKE REVASKULARIZACIJE KAROTIDNE ARTERIJE U ODNOSU NA KLINIČKU MANIFESTACIJU BOLESTI

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Abstract

Introduction. Open surgical carotid artery revascularization remains the gold standard for the treatment of carotid atherosclerotic disease. The aim of this study was to analyze atherosclerotic risk factors in patients undergoing open surgical carotid revascularization and to evaluate intraprocedural factors associated with periprocedural complications. **Material and Methods.** This retrospective study included 125 patients treated at the University Clinical Center of Vojvodina between 2023 and 2024. Data were collected from medical records at the Clinic for Vascular and Endovascular Surgery. **Results.** Patients were categorized as asymptomatic (n = 89) and symptomatic (n = 36). The study population consisted of 63% men and 37% women. An incomplete Circle of Willis was observed in 24% of patients (16% in the asymptomatic group and 44% in the symptomatic group), demonstrating a significant association with disease stage (p = 0.001). Unstable plaques were detected in 15% of asymptomatic and 36.1% of symptomatic patients (p = 0.023). An incomplete Circle of Willis was significantly associated with the occurrence of hyperperfusion syndrome (p = 0.012) and intraoperative hypertension (p < 0.001). **Conclusion.** Age, cardiac comorbidities, plaque morphology, and completeness of the Circle of Willis are associated with the clinical stage of extracranial cerebrovascular disease. Intraoperatively, hemodynamic instability, carotid plaque length, clamp duration, and total procedure time were associated with an increased risk of procedural complications.

Key words: Cerebrovascular Disorders; Endarterectomy, Carotid; Surgical Procedures, Operative; Postoperative Complications; Treatment Outcome; Plaque, Atherosclerotic; Atherosclerosis; Risk Factors

Sažetak

Uvod. Otvorena hirurška revaskularizacija predstavlja zlatni standard lečenja karotidne aterosklerotske bolesti. Cilj rada bila je analiza faktora rizika ateroskleroze kod ispitanika nakon otvorene hirurške revaskularizacije karotidnih arterija; analiza uticaja intraproceduralnih faktora na periproceduralne komplikacije. **Materijal i metode.** Retrospektivna studija obuhvatila je 125 ispitanika lečenih u Univerzitetskom kliničkom centru Vojvodine u periodu 2023–2024. godine. Podaci su prikupljeni iz medicinske dokumentacije Klinike za vaskularnu i endovaskularnu hirurgiju. **Rezultati.** Ispitanici su podeljeni na one bez simptoma (asimptomatske) (n = 89) i one sa simptomima (simptomatske) (n = 36). Ukupno 63% je bilo muškog, a 37% ženskog pola. Inkompletan Vilisov šestougao utvrđen je kod 24% ispitanika (16% asimptomatskih i 44% simptomatskih), uz značajnu razliku u odnosu na klinički stadijum (p = 0,001). Nestabilan plak bio je prisutan kod 15% asimptomatskih i 36,1% simptomatskih ispitanika (p = 0,023). Hiperperfuzioni sindrom bio je povezan sa inkompletnim Vilisovim šestouglom (p = 0,012) i intraoperativnom hipertenzijom (p < 0,001). **Zaključak.** Starost, kardiološka bolest, morfologija plaka i kompletnost Vilisovog šestougla značajno koreliraju sa stadijumom ekstrakranijalne cerebrovaskularne bolesti. Intraoperativno, hemodinamička nestabilnost, dužina plaka, trajanje kleme i trajanje intervencije povezani su sa proceduralnim komplikacijama.

Ključne reči: cerebrovaskularna bolest; karotidna endarterektomija; operativne hirurške procedure; postoperativne komplikacije; ishod lečenja; aterosklerotski plak; ateroskleroza; faktori rizika

Introduction

Open surgical carotid artery revascularization, or carotid endarterectomy (CEA), remains the gold standard for the treatment of both symptomatic and asymptomatic carotid atherosclerotic disease [1]. In approximately 60-80% of cases, atherosclerotic lesions of the extracranial carotid arteries lead to re-

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Abbreviations

BMI – body mass index
CAS – carotid artery stenting
CEA – carotid endarterectomy
CoW – Circle of Willis
COPD – chronic obstructive pulmonary disease
DM – diabetes mellitus
EEA – eversion endarterectomy
HLP – hyperlipoproteinemia/hyperlipidemia
HPS – cerebral hyperperfusion syndrome
HTA – arterial hypertension
PAOD – peripheral arterial occlusive disease
TEA – conventional endarterectomy
TIA – transient ischemic attack
UKCV – University Clinical Center of Vojvodina

duced cerebral blood flow, thereby creating an opportunity for preventive surgical intervention [2].

Contemporary approaches to carotid artery disease and stroke – particularly ischemic stroke – emphasize the importance of timely intervention as the most critical factor in preventing irreversible neuronal damage [3]. The incidence of stroke continues to increase in both elderly and younger populations and remains associated with high mortality and a substantial socioeconomic burden. Current therapeutic strategies include preventive, pharmacological, and surgical approaches [4,5].

Preventive strategies can be divided into primary prevention – focused on identifying and modifying risk factors such as smoking, physical inactivity, and poor dietary habits – and secondary prevention, which aims to reduce the risk of stroke recurrence in patients with a history of stroke or transient ischemic attacks (TIA) [6,7].

Pharmacological therapy targets comorbid conditions that contribute to the development or progression of carotid atherosclerosis. Commonly used medications include antiplatelet agents such as aspirin and clopidogrel, statins, and anticoagulants such as warfarin or heparin [8].

Endovascular revascularization techniques include carotid artery stenting (CAS), which represents a less invasive alternative to open surgery and is typically reserved for patients considered to be at higher surgical risk [9].

Open surgical revascularization through CEA restores hemodynamically adequate carotid flow [10]. CEA can be performed using either the eversion endarterectomy (EEA) technique or the conventional technique (TEA), with or without the use of a shunt, depending on the surgeon's preference [10].

The aim of this study was to analyze the type and frequency of atherosclerotic risk factors in patients undergoing open surgical carotid revascularization according to the clinical stage of extracranial cerebrovascular disease, and to evaluate the impact of intraprocedural factors on the occurrence of periprocedural complications.

Material and Methods

This retrospective study included 125 patients who underwent open surgical carotid revascularization at the University Clinical Center of Vojvodina (UKCV) between January 2023 and December 2024. Data were obtained from the medical records of the Clinic for Vascular and Endovascular Surgery, UKCV, Novi Sad, including electronic database, operative reports, clinical and radiological documentation, and discharge summaries.

All procedures were performed by vascular surgeons. Postoperatively, patients were monitored in the intensive care unit and subsequently transferred to the surgical ward. Patients with an uncomplicated postoperative course were discharged on the fourth postoperative day.

Inclusion criteria were: age >18 years; carotid artery stenosis of 70-99% with an indication for open surgical revascularization; and absence of focal neurological deficits (including ischemic stroke, transient ischemic attack, or amaurosis fugax) attributable to the ipsilateral carotid artery within the preceding six weeks.

Exclusion criteria included: occlusion of the carotid artery planned for treatment; severe or unstable comorbid conditions; extreme preoperative blood pressure values; symptomatic patients with typical carotid-related neurological symptoms within the preceding six weeks; significant intracranial vascular pathology; and incomplete medical documentation.

During surgery, carotid clamp duration was recorded and plaque morphology was documented. Heparin was administered at a dose of 100 IU/kg [11]. Protamine was not routinely used.

The following procedural complications were analyzed: new-onset neurological deficit, myocardial infarction or death, bleeding and wound hematoma, hemodynamic instability (hypotension or hypertension, tachycardia, bradycardia), arrhythmia, delirium, hyperperfusion syndrome, cranial nerve injury, and carotid artery thrombosis occurring within 30 days.

Hyperperfusion syndrome (HPS) was defined as the occurrence of clinical manifestations such as migraine-like headache, ophthalmalgia, facial neuralgia, seizures, and focal neurological deficits resulting from cerebral edema or intracranial hemorrhage [12].

Descriptive and comparative statistical analyses were performed between the asymptomatic and symptomatic patient groups. Categorical variables were analyzed using the chi-square test, while continuous variables were assessed using the independent samples t-test. Significance was defined as $p < 0.05$.

Table 1. Prevalence of risk factors in the sample

Risk Factor	Overall Prevalence (%)	Asymptomatic Group (%)	Symptomatic Group (%)
Diabetes mellitus	34	29	44
Hyperlipidemia	71	73	67
Hypertension	97	99	92
Chronic kidney disease	5.2	2.3	5.6
Peripheral arterial occlusive disease	20.8	19	25
Chronic obstructive pulmonary disease	13	11.2	16.7
Cardiac arrhythmia	17.6	18	17
Cardiac disease	30	36	14
Obesity	9.6	11.2	5.6

Table 2. Postoperative complications

Complication	Total (%)	Asymptomatic (%)	Symptomatic (%)
Hematoma	3.2	5.6	11.1
Infection	0.8	0	2.8
Thrombosis	1.6	1.1	2.8
Stroke	2.4	1.1	5.6
Transient ischemic attack	4	2.2	8.3
Hyperperfusion syndrome	12	10.1	16.7
In-hospital mortality	0.8	0	2.8
Acute myocardial infarction	0.8	0	2.8
Delirium	2.4	3.4	0
Postprocedural hypertension	20	15.7	30.6
Postprocedural hypotension	5.6	5.6	5.6
Arrhythmia	2.4	1.1	5.6
Cranial nerve injury	8	7.9	8.3

Results

Between January 2023 to December 2024, open surgical carotid revascularization was performed in 225 patients at UKCV. Of these, 125 patients who met the inclusion criteria were enrolled in the study to ensure group homogeneity. Patients were categorized as asymptomatic (n = 89) or symptomatic (n = 36).

The study population included 79/125 (63%) men and 46/125 (37%) women. No statistically significant association was found between sex and the clinical stage of the disease ($\chi^2(1) = 0.094$; $p = 0.759$).

Patient age ranged from 47 to 81 years, with a mean age of 64 ± 7 years. Asymptomatic patients were significantly older (66 ± 6.43 years) than symptomatic patients (64 ± 7.27 years; $p < 0.001$).

The most common risk factors are presented in **Table 1.** Chi-square analysis revealed a statistically significant difference according clinical stage for cardiac disease, which was more frequent observed in asymptomatic subjects ($\chi^2(1) = 4.997$; $p = 0.025$).

The right carotid artery was treated in 50.4% of patients and the left carotid artery in 49.6%, with no statistically significant difference between the groups.

An incomplete Circle of Willis (CoW) was identified in 24% of patients (16% of asymptomatic and 44% of symptomatic patients), demonstrating a statistically significant association with the clinical stage of the disease ($\chi^2(1) = 10.066$; $p = 0.001$).

Unstable plaque morphology was present in 21.6% of patients: 15% of asymptomatic and 36.1% of symptomatic patients ($\chi^2(1) = 5.141$; $p = 0.023$). The mean plaque length of internal carotid artery was significantly greater in symptomatic subjects ($p < 0.001$).

Postoperative complications are summarized in **Table 2,** while comparative analyses of selected complications are presented in **Tables 3-6**. Carotid thrombosis occurring within 30 days was significantly associated with the severity of contralateral carotid stenosis ($p = 0.021$) **(Table 3).** Hyperperfusion syndrome showed a significant association with incomplete CoW ($p = 0.012$) and intraoperative hypertension ($p < 0.001$) **(Table 4).** Postoperative hypertension was significantly associated with intraoperative hypertension ($p < 0.001$), whereas postoperative hypotension was associated with preoperative hypertension ($p = 0.005$) and intraoperative hypotension ($p = 0.010$) **(Table 5).** Postoperative arrhythmia

Table 3. Thrombosis within 30 days – comparative variables (selected)

Variable	Chi-square	df	p
Sex	0.122	1	0.727
Diabetes mellitus	0.067	1	0.795
ECST stenosis (contralateral)	7.689	2	0.021*
Operative technique	0.404	2	0.817

ECST = European Carotid Surgery Trial; *p <0.05

Table 4. Hyperperfusion syndrome – comparative variables (selected)

Variable	Chi-square	df	p
Sex	0.313	1	0.576
Diabetes mellitus	0.805	1	0.370
Incomplete Circle of Willis	6.317	1	0.012*
Intraoperative hypertension	17.526	1	<0.001*

*p <0.05

Table 5. Postoperative hypotension with comparative variables

Postoperative hypotension	χ^2	df	
Gender	0.000	1.000	1.000
DM	0.000	1.000	1.000
HLP	0.000	1.000	1.000
HTA	**7.954**	**1.000**	**0.005***
Nicotinismus	0.203	2.000	0.903
CRI	0.372	1.000	0.542
PAOD	0.000	1.000	1.000
COPD	0.213	1.000	0.645
Heart rhythm disorder	0.559	1.000	0.455
Cardiac disease	0.133	1.000	0.715
Obesity BMI +35	0.052	1.000	0.820
Side of the carotid artery	0.000	1.000	1.000
Asymptomatic/symptomatic	0.000	1.000	1.000
Anticoagulant therapy	0.213	1.000	0.645
Medication administration	0.218	2.000	0.897
Is CoW complete	0.000	1.000	1.000
ECST grade of treated carotid stenosis	0.000	1.000	0.983
ECST grade of contralateral carotid stenosis	1.194	2.000	0.551
Contralateral carotid occlusion	0.000	1.000	1.000
Plaque type	0.000	1.000	0.991
Type of operative technique	1.287	2.000	0.525
Anesthesia	0.993	1.000	0.319
Intraoperative hypotension	**6.598**	**1.000**	**0.010***
Intraoperative hypertension	0.317	1.000	0.574
Intraoperative bradycardia HR below 40/min	0.000	1.000	1.000
Tachycardia intraoperative HR over 100/min	0.000	1.000	1.000
Javid's shunt	0.381	1.000	0.537
Dose of heparin	0.330	1.000	0.566
Protamine	0.025	1.000	0.873

DM – diabetes mellitus; HLP – hyperlipoproteinemia; HTA – arterial hypertension; Nicotinismus-smoking; CRI – chronic renal insufficiency; PAOD – peripheral arterial occlusive disease; COPD – chronic obstructive pulmonary disease, BMI – body mass index; CoW-Willis hexagon; HR – heart rate

was significantly associated with the operative technique used (p = 0.010) **(Table 6).**

Table 6. Postoperative arrhythmia with comparative variables

Postoperative rhythm disorder-arrhythmia	χ^2	df	p
Gender	0.000	1.000	1.000
DM	0.000	1.000	1.000
HLP	0.000	1.000	1.000
HTA	0.000	1.000	1.000
Nicotinismus	0.455	2.000	0.797
CRI	0.000	1.000	1.000
PAOD	0.000	1.000	1.000
COPD	0.041	1.000	0.839
Heart rhythm disorder	0.000	1.000	1.000
Cardiac disease	0.000	1.000	1.000
Obesity BMI +35	0.000	1.000	1.000
Side of the carotid artery	1.334	1.000	0.248
Asymptomatic/symptomatic	0.674	1.000	0.412
Anticoagulant therapy	0.041	1.000	0.839
Medication administration	1.790	2.000	0.409
Is CoW complete	0.000	1.000	1.000
ECST grade of treated carotid stenosis	0.000	1.000	0.989
ECST grade of contralateral carotid stenosis	0.847	2.000	0.655
Contralateral carotid occlusion	0.000	1.000	1.000
Plaque type	0.044	1.000	0.834
Type of operative technique	**9.237**	**2.000**	**0.010***
Anesthesia	0.000	1.000	1.000
Intraoperative hypotension	1.139	1.000	0.286
Intraoperative hypertension	0.000	1.000	1.000
Intraoperative bradycardia HR below 40/min	0.000	1.000	1.000
Tachycardia intraoperative HR over 100/min	0.000	1.000	1.000
Javid's shunt	0.000	1.000	1.000
Dose of heparin	0.506	1.000	0.477
Protamine	0.000	1.000	1.000

DM – diabetes mellitus; HLP – hyperlipoproteinemia; HTA – arterial hypertension; Nicotinismus-smoking; CRI – chronic renal insufficiency; PAOD – peripheral arterial occlusive disease; COPD – chronic obstructive pulmonary disease, BMI – body mass index; CoW-Willis hexagon; HR – heart rate

Discussion

The age distribution observed in our study (47-81 years; mean 64 ± 7 years) is consistent with contemporary literature indicating that clinically significant carotid stenosis most frequently manifests in the seventh decade of life [13,14]. Interestingly, asymptomatic patients in our cohort were significantly older than symptomatic patients ($p < 0.001$), suggesting that carotid atherosclerosis may progress gradually in older individuals without acute neurological manifestations. This observation highlights the importance of preventive screening in elderly populations.

The predominance of male patients (63%) corresponds with the well-established epidemiological profile of carotid artery disease [15]. Although sex was not significantly associated with the clinical stage of the disease ($p = 0.759$), consistent with findings reported by Schmid et al. [16], it remains an important demographic variable in cardiovascular risk stratification.

Analysis of risk factors revealed a high prevalence of systemic atherosclerotic conditions in the study population, including diabetes mellitus (34%), hyperlipidemia (71%), and hypertension (97%). Notably, cardiac disease was significantly more prevalent in asymptomatic subjects ($p = 0.025$). This finding, also reported by Pastori et al. [17], suggests that patients with established cardiac disease should undergo routine carotid screening even in the absence of neurological symptoms, in order to reduce the risk of ischemic stroke.

A central aspect of our study was the analysis of anatomical variations of the CoW. An incomplete CoW was identified in 24% of patients, with a significantly higher prevalence among symptomatic individuals

(44% vs. 16%; p = 0.001). Reported rates of CoW completeness vary widely in the literature (3.5-63%) [18]. Nevertheless, our findings support the hypothesis that incomplete collateral circulation may increase the risk of neurological symptoms and ischemic events due to limited compensatory cerebral blood flow.

Plaque morphology also proved to be an important determinant of clinical presentation. Unstable plaques were significantly more common in symptomatic patients (36.1% vs. 15%; p = 0.023), supporting the well-established concept that such plaques are more prone to rupture and distal embolization [20]. Furthermore, plaque length was significantly greater in symptomatic patients (p < 0.001), in agreement with Ball et al. [21], suggesting that greater atherosclerotic burden is associated with increased risk of cerebral ischemia.

Regarding intraoperative factors, the use of an intraluminal shunt in 32% of patients (42% of symptomatic patients) reflects our institutional strategy aimed at maximizing cerebral protection during carotid cross-clamping. This rate is somewhat higher than that reported by several international centers. Postprocedural hemodynamic disturbances, particularly peak systolic pressure variations, were strongly influenced by intraoperative hemodynamic status. HPS observed in 12% of patients, was significantly associated with intraoperative hypertension (p < 0.001) and incomplete CoW (p = 0.012). Although the incidence of HPS in our cohort exceeds the rates reported in meta-analyses (0-3%) [22], the observed relationship with CoW anatomy and blood pressure control is consistent with existing literature [23,24].

Cranial nerve injury, observed in 8% of patients, most frequently involved the recurrent laryngeal nerve, while postoperative delirium occurred in 2.4% of patients. These complications underscore the importance of continued refinement of surgical techniques and anesthetic management. Our results suggest that plaque length may increase the risk of nerve injury [25], whereas the use of EEG-guided anesthesia has been proposed as a strategy to reduce postoperative delirium.

Finally, carotid thrombosis within 30 days (1.6%) as significantly associated with the severity of contralateral carotid stenosis (p = 0.021), highlighting the importance of evaluating global cerebral perfusion status undergoing carotid revascularization. Interestingly, patients who developed this complication were younger on average, cohort finding that warrants further investigation, as similar associations have rarely been reported in the available literature.

Conclusion

The analysis of comorbidities and preoperative factors indicates that age, cardiac disease, plaque morphology, and the completeness of the Circle of Willis are significantly associated with the clinical stage of extracranial cerebrovascular disease. Furthermore, evaluation of intraoperative variables demonstrates that hemodynamic instability, operative technique, clamp duration, and internal carotid artery plaque length are significantly associated with the occurrence of procedural complications. Overall, open surgical carotid revascularization remains highly effective treatment modality for carotid occlusive disease, achieving favorable outcomes with low rates of periprocedural morbidity and mortality.

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PERIOPERATIVE OUTCOME FOLLOWING OPEN SURGICAL REPAIR OF SYMPTOMATIC NON-RUPTURED ABDOMINAL AORTIC ANEURYSM

PERIOPERATIVNI ISHOD NAKON OTVORENOG HIRURŠKOG LEČENJA SIMPTOMATSKE NERUPTURIRANE ANEURIZME ABDOMINALNE AORTE

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Abstract

Introduction. Symptomatic non-ruptured abdominal aortic aneurysm represents an intermediate clinical entity between elective aneurysms and ruptured disease. This study aimed to compare perioperative outcomes and the incidence of acute kidney injury incidence between patients undergoing open surgical repair for symptomatic versus asymptomatic abdominal aortic aneurysms. **Material and Methods.** This retrospective cohort study included 178 patients who underwent open surgical repair for infrarenal abdominal aortic aneurysm between January 2021 and January 2023. Patients were classified as symptomatic (n = 60) if they presented with abdominal or back pain, limb ischemia without rupture, and as asymptomatic (n = 118) if treated electively. Demographic characteristic, comorbidities, intraoperative parameters, and postoperative outcomes were analyzed. **Results.** Symptomatic patients had a significantly larger mean aneurysm diameter compared with asymptomatic patients (74.5 vs. 64.2 mm; p < 0.001). Overall postoperative complications occurred more frequently in symptomatic patients (28.3% vs. 9.3%; p = 0.001), particularly cardiac complications (10% vs. 2.5%; p = 0.032). The length of hospital stay was significantly longer in the symptomatic group (10.1 vs. 8.4 days; p = 0.004). The incidence of postoperative acute kidney injury did not differ significantly between groups (31.7% vs. 27.1%; p = 0.53). However, preoperative chronic kidney disease and anemia were strong predictors of postoperative acute kidney injury. Thirty-day mortality was higher in symptomatic patients (8.3% vs. 3.4%) although the difference did not reach statistical significance (p = 0.40). **Conclusion.** Symptomatic non-ruptured abdominal aortic aneurysm is associated with larger aneurysm size, higher complication rates, and prolonged hospitalization. Nevertheless, open surgical repair can be performed with acceptable outcomes in specialized centers.

Key words: Aortic Aneurysm, Abdominal; Vascular Surgical Procedures; Treatment Outcome; Postoperative Complications; Risk Factors; Acute Kidney Injury; Renal Insufficiency, Chronic

Sažetak

Uvod. Simptomatska nerupturirana aneurizma abdominalne aorte predstavlja intermedijarni klinički entitet između elektivne i rupturirane bolesti. Ova studija je uporedila perioperativne ishode i incidenciju akutnog bubrežnog oštećenja između pacijenata koji su podvrgnuti otvorenoj hirurškoj reparaciji simptomatske u odnosu na asimptomatsku aneurizmu abdominalne aorte. **Materijal i metode.** Ova retrospektivna kohortna studija uključila je 178 pacijenata koji su podvrgnuti otvorenoj hirurškoj reparaciji infrarenalne aneurizme abdominalne aorte između januara 2021. i januara 2023. godine. Pacijenti su klasifikovani na one sa simptomima (simptomatski) (n = 60), ako su se prezentovali sa bolom ili ishemijom udova bez rupture, i na one bez simptoma (asimptomatski) (n = 118) ako su lečeni elektivno. Analizirani su demografski podaci, komorbidoteti, intraoperativni parametri i postoperativni ishodi. **Rezultati.** Simptomatski pacijenti imali su značajno veći srednji dijametar aneurizme (74,5 naspram 64,2 mm, p < 0,001). Ukupne postoperativne komplikacije javljale su se češće kod simptomatskih pacijenata (28,3% naspram 9,3%, p = 0,001), posebno kardijalne komplikacije (10% naspram 2,5%, p = 0,032). Bolničko lečenje bilo je značajno duže u simptomatskoj grupi (10,1 naspram 8,4 dana, p = 0,004). Incidencija akutnog bubrežnog oštećenja nije se značajno razlikovala između grupa (31,7% naspram 27,1%, p = 0,53). Međutim, preoperativna hronična bubrežna bolest i anemija bile su snažni prediktori postoperativnog akutnog bubrežnog oštećenja. Tridesetodnevni mortalitet bio je viši u grupi sa simptomima (8,3% naspram 3,4%) ali nije dostigao statističku značajnost (p = 0,40). **Zaključak.** Simptomatska nerupturirana aneurizma abdominalne aorte povezana je sa većom veličinom aneurizme, višom stopom komplikacija i produženom hospitalizacijom. Otvorena hirurška reparacija može se izvoditi sa prihvatljivim ishodima u specijalizovanim centrima.

Ključne reči: aneurizma abdominalne aorte; vaskularne hirurške procedure; ishod lečenja; postoperativne komplikacije; faktori rizika; akutno oštećenje bubrega; hronična bubrežna insuficijencija

Introduction

Abdominal aortic aneurysm (AAA) is a progressive degenerative disease of the aortic wall characterized by chronic inflammation, extracellular matrix degeneration, and gradual dilatation of the vessel. With the increasing use of ultrasound and other imaging modalities, most AAAs are currently detected

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Abbreviations

AAA	– abdominal aortic aneurysm
AKI	– acute kidney injury
AsAAA	– asymptomatic abdominal aortic aneurysm
CI	– confidence interval
CKD	– chronic kidney disease
CMP	– cardiomyopathy
COPD	– chronic obstructive pulmonary disease
CRF	– chronic renal failure
DM	– diabetes mellitus
eGFR	– estimated glomerular filtration rate
EVAR	– endovascular aneurysm repair
HLP	– hyperlipoproteinemia
HTA	– arterial hypertension
KDIGO	– Kidney Disease: Improving Global Outcomes
OR	– odds ratio
OSR	– open surgical repair
SAAA	– symptomatic non-ruptured abdominal aortic aneurysm
SD	– standard deviation
MACE	– Major Adverse Cardiac Events
MGS/MGS-2	– Melbourne Group Scale
MARE	– Major Adverse Respiratory Events

incidentally. These patients are predominantly asymptomatic (AsAAA) and are managed according to established size- and risk-based clinical guidelines [1–3].

However, a subset of patients present with abdominal, back, or flank pain, distal embolization, or signs of local compression without radiological evidence of rupture. These symptomatic non-ruptured aneurysms (SAAA) represent an intermediate yet clinically important category between elective aneurysms and urgent presentations such as ruptured AAA [4–6]. Several studies suggest that the onset of new symptoms may indicate aneurysm instability, rapid expansion, or impending rupture, and may therefore be associated with worse perioperative outcomes compared with AsAAA [4,5,7].

Open surgical repair (OSR) remains a fundamental treatment modality for AAA, particularly in patients with unfavorable anatomy for endovascular aneurysm repair, in younger individuals, and in centers with strong expertise in open vascular surgery [1,8,9]. Although outcomes after elective OSR have been extensively studied, evidence regarding perioperative risk in patients with SAAAs remains less consistent. Large cohort studies have identified symptomatic presentation as an independent predictor of perioperative morbidity and mortality. However, most previously published studies combine symptomatic and ruptured aneurysms, analyze heterogeneous populations undergoing both open and endovascular repair, or lack detailed intraoperative and postoperative data required for accurate risk stratification [4–6].

Acute kidney injury (AKI) represents one of the most clinically significant postoperative complications following AAA repair. It occurs in up to one-third of patients undergoing open repair and is strongly associated with increased short-term morbidity, prolonged intensive care unit stay, the need for renal replacement therapy, and increased long-term mortality. Patients with SAAA may be particularly susceptible to renal injury due to hemodynamic instability, microembolization, higher transfusion requirements, or more complex surgical exposure. Although several studies have evaluated AKI following elective or ruptured AAA repair [10–13], few have specifically examined whether symptomatic presentation itself increases the risk of postoperative renal dysfunction in patients undergoing OSR. This represents an important knowledge gap, as AKI substantially affects both early and long-term outcomes after aortic surgery.

Taken together, the current literature suggests that symptomatic non-ruptured AAAs represent a distinct and clinically relevant subgroup with potentially worse perioperative and long-term outcomes, yet high-quality evidence focusing specifically on open surgical repair remains limited. A clearer understanding of how symptomatic presentation influences postoperative complications, acute kidney injury, and survival is essential for optimizing patient selection, perioperative risk counseling, and management strategies.

The objective of this study was to compare perioperative outcomes, the incidence of acute kidney injury, and short-term survival in patients undergoing open surgical repair for symptomatic non-ruptured versus asymptomatic abdominal aortic aneurysms over a three-year period in a high-volume vascular surgery center. Additionally, the study aimed to identify independent predictors of postoperative morbidity, mortality, and renal dysfunction, with particular emphasis on variables associated with symptomatic presentation.

Material and Methods

This retrospective cohort study included 178 patients who underwent open surgical repair (OSR) for abdominal aortic aneurysm (AAA) at the University Clinical Center of Vojvodina, Serbia between January 2021 and January 2023. Of these, 60 patients underwent surgery for symptomatic non-ruptured abdominal aortic aneurysm (SAAA), while 118 patients received elective treatment for asymptomatic abdominal aortic aneurysm (AsAAA). Patients were classified as having SAAA if they presented with abdominal, back, or groin pain attributable to the aneurysm, or limb ischemia, without radiologic or intraoperative evidence of rupture. Asymptomatic patients underwent elective repair based on aneurysm size or documented aneurysm growth. Baseline demographic and clinical variables, aneurysm characteristics, intraoperative parameters, and postoperative outcomes were extracted from electronic and paper records of the institutional medical registry at the

University Clinical Center of Vojvodina. The following preoperative variables were collected: age, sex, aneurysm diameter, comorbidities: arterial hypertension (HTA), cardiomyopathy (CMP), chronic obstructive pulmonary disease (COPD), hyperlipoproteinemia (HLP)], diabetes mellitus (DM), and chronic kidney disease (CKS), cigarette smoking, estimated glomerular filtration rate (eGFR), hemoglobin level, and presenting symptoms.

The following intraoperative and postoperative parameters were recorded:

– Surgical technique (interposition of Dacron tube graft, aortobiiliac bypass, or aortobifemoral bypass)
– Intraoperative blood loss (ml)
– Duration of surgery (minutes)
– Treatment outcome
– Postoperative complications were defined as local or systemic complications occurring during hospitalization or within 30 days after surgery. Cardiac complications were defined according to Major Adverse Cardiac Events (MACE) criteria and included: acute myocardial infarction, new-onset cardiac arrhythmia requiring treatment, acute heart failure, and cardiac death. Pulmonary complications were defined according to Major Adverse Respiratory Events (MARE) criteria using the Melbourne Group Scale (MGS/MGS-2). These included: respiratory failure requiring supplemental oxygen or mechanical ventilation beyond baseline, pneumonia (new radiological infiltrate accompanied by fever, purulent sputum, or positive microbiological culture), atelectasis requiring bronchoscopy or physiotherapy, pleural effusion requiring drainage, and pneumothorax.
– Acute kidney injury (AKI) defined according to KDIGO criteria, and the need for renal replacement therapy
– Duration of hospitalization
– Overall survival (30-day mortality)

All procedures were performed in the operating rooms of the University Clinical Center of Vojvodina and the Emergency Center in Novi Sad. Surgical interventions were carried out collaboratively by vascular surgeons and anesthesiologists, and all patients underwent general endotracheal anesthesia. Following surgery, patients were transferred to the Intensive Care Unit and subsequently to the Department of Vascular and Endovascular Surgery. After clinical stabilization and recovery, patients were discharged with prescribed medications and scheduled follow-up visits.

Statistical Analysis

All data were entered into a database and analyzed using appropriate statistical methods. Continuous variables are presented as mean ± standard deviation (SD) and were compared between groups using the Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed variables. Categorical variables are presented as frequencies and percentages and were compared using the Pearson chi-squared test or Fisher's exact test, as appropriate. Logistic regression analysis was performed to identify independent predictors of postoperative acute kidney injury. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). A p-value < 0.05 was considered statistically significant.

The study was approved by the Ethics Committee of the Faculty of Medicine, Novi Sad, and all procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Results

The study included 178 patients with infrarenal AAA who underwent OSR. Of these, 60 patients (33.7%) underwent surgery in emergency or delayed settings for SAAA, whereas 118 patients (66.3%) underwent elective OSR. Patients with confirmed AAA rupture, aortocaval fistula, or aortoduodenal fistula were excluded from the analysis.

Table 1. Gender, age, and comorbidity distribution of patients with abdominal aortic aneurysm

	SAAA	AsAAA	P value
Number of patients	60	118	-
Male	81.7% (49/60)	81.3% (96/118)	0.96
Average age, years	73.7 years (57-89) SD 6.7	71.9 years (55-85) SD 6.1	0.07
Hypertension	83.3% (50/60)	91.5% (108//118)	0.102
Hyperlipoproteinemia	21.7% (13/60)	11.9% (14/118)	0.085714
Chronic obstructive pulmonary disease	15% (9/60)	27.1% (32/118)	0.781
Diabetes mellitus	36.6% (22/60)	11.9% (14/118)	0.0000001
Cardiomyopathy	18.3% (11/60)	43.7% (56/118)	0.000121
Cigarette use	10% (6/60)	32.2% (38/118)	0.001066
Chronic kidney disease	30% (18/60)	18.6% (22/118)	0.0871
eGFR mL/min/1.73 m^2	102 SD 25.6	105,2 SD 20.3	0.356
Size of aneurysm, mm	74.5 mm SD 15.7	64.2 mm SD 9.8	0.0000000293

The majority of patients in both groups were male (SAAA: 81.7%; AsAAA 81.3%), with no statistically significant difference in sex distribution between the groups **(Table 1).**

The mean age was slightly higher in the SAAA group compared with the AsAAA group, although this difference did not reach statistical significance (SAAA: 73.7 years, SD 6.7; AsAAA: 71.9 years, SD 6.1; p = 0.07). The oldest patient was 89 years old, and the youngest was 55 years old.

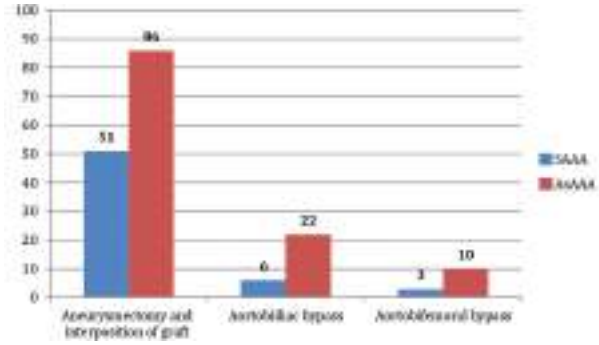
The mean aneurysm diameter was 74.5 mm (SD 15.7) in the SAAA group and 64.2 mm (SD 9.8) in the AsAAA group. Patients treated for SAAA had significantly larger aneurysms (p < 0.001).

Baseline characteristics and comorbidities are presented in **Table 1.** The most common comorbidity in both groups was arterial hypertension (HTA) (SAAA: 83.3%, AsAAA 91.5%; p = 0.10). Diabetes mellitus (DM) was significantly more prevalent in the SAAA group (36.6% vs. 11.9%, p < 0.001), whereas cigarette smoking (10% vs. 32.2%, p = 0.001) and cardiomyopathy (CMP) (18.3% vs. 43.7%, p<0.001) were more common in the AsAAA group. Chronic kidney disease (CKD) was present in 30% of SAAA patients and 18.6% of AsAAA patients (p = 0.0871).

All patients underwent open surgical repair. Aneurysmectomy with interposition of a Dacron tube graft was the most frequently performed procedure in both groups (SAAA: 85%, 51/60; AsAAA: 72.9%, 86/118), followed by aortoiliac bypass (SAAA: 10%, 6/60; AsAAA: 18.6%, 22/118) and aortobifemoral bypass (SAAA: 5%, 3/60; AsAAA: 8.5%, 10/118) **(Graph 1).**

Perioperative blood loss and operative duration were comparable between groups **(Table 2)**. Mean intraoperative blood loss was 1159 ml (SD 662) in the SAAA and 1112 ml (SD 673) in the AsAAA (p = 0.65). Mean operative time was 147 minutes (SD 37) in the SAAA and 144 minutes (SD 49) in the AsAAA (p = 0.68).

Total postoperative complications were significantly more frequent in the SAAA group (28.3% vs. 9.3%, p = 0.001), particularly cardiac complications (10% vs. 2.5%, p = 0.032). Pulmonary complications (10% vs. 3.3%, p = 0.071) and local complications (5% vs. 2.5%, p = 0.39) did not differ significantly between the groups.



Graph 1. Applied surgical techniques

Acute kidney injury (AKI) occurred in 31.7% of SAAA patients (19/60) and 27.1% of AsAAA patients (32/118), with no statistically significant difference between the groups (p = 0.53). However, postoperative AKI was significantly more frequent in patients with preoperative CKD (73% vs. 20%, p < 0.001) and in those with preoperative anemia (69% vs. 22%, p < 0.05). Preoperative CKD (OR 10.5, 95% CI 4.0-27.5) and anemia (OR 9.5, 95% CI 3.5-22.5) were strong predictors of postoperative AKI.

The length of hospital stay was significantly longer in the SAAA group (mean 10.1 days, SD 3.7) compared to the AsAAA group (mean 8.4 days, SD 3.6; p = 0.004). This difference likely reflects the higher complication rate and the need for preoperative stabilization in symptomatic patients.

Thirty-day mortality was higher in the SAAA group (8.3%, 5/60) than in the AsAAA group (3.4%, 4/118), although this difference did not reach statistical significance (p = 0.40).

Discussion

Abdominal aortic aneurysm (AAA) remains a major cause of cardiovascular morbidity and mortality worldwide, with an estimated prevalence of 2–8% in men older than 65 years. Women tend to experience

Table 2. Comparative analysis of intraoperativly and postoperatively monitored parameters

	SAAA	AsAAA	P value
Intraoperative blood lose	1159 ml SD 662 ml	1112 ml SD 673 ml	0.65
Duration of surgery	147 min SD 37 min	144 min SD 49 min	0.68008
Postoperative complications	28.3% (17/60)	9.3% (11/118)	0.00122
Local complications	5% (3/60)	2.5% (3/118)	0.392
Cardiac complications	10% (6/60)	2.5% (3/118)	0.03191
Pulmonary complications	10% (6/60)	3.3% (4/118)	0.070911
Acute kidney injury	31.7% (19/60)	27.1% (32/118)	0.528508
Hospital stay	10.1 days SD 3.7	8.4 days SD 3.6	0.003958
30 day mortality	8.3% (5/60)	3.4%(4/118)	0.3976

aneurysm rupture at smaller diameters and generally have poorer clinical outcomes compared with men [1,2].

Despite significant improvements in screening programs and elective repair, ruptured AAA continues to be associated with extremely poor prognosis, with overall mortality exceeding 80%, largely due to prehospital deaths. Even with emergency surgery is performed, perioperative mortality remains high [1, 14–16]. Consequently, ruptured AAA accounts for approximately 1–2% of all deaths in men older than 65 years in Western countries.

Within this clinical spectrum, symptomatic non-ruptured AAA (SAAA) represents a distinct and clinically important category positioned between elective asymptomatic aneurysms and ruptured disease. Previous studies have demonstrated that SAAA is associated with perioperative mortality and complication rates that are intermediate between these elective and ruptured AAA, highlighting its unique risk profile and the need for focused evaluation [17].

In the present study, patients with SAAA tended to be older than those undergoing elective repair, although the difference did not reach statistical significance. Similar observations have been reported by Mroczek et al. [18] and De Martino et al. [19], although some studies found no significant age difference [5]. As expected, maximum aneurysm diameter was significantly larger in the symptomatic group, a finding consistently reported in the literature [18–23].

With regard to comorbidities, diabetes mellitus was more prevalent in the SAAA group, whereas cardiomyopathy and active smoking were more frequently observed in asymptomatic patients, possibly reflecting surveillance-driven diagnosis in these high-risk individuals. These findings contrast with some studies reporting higher smoking rates and greater prevalence of cardiomyopathy among patients with SAAA [5,7, 18,19], which may reflect cohort differences. Arterial hypertension was the most common comorbidity in both groups, underscoring its well-established role in AAA pathogenesis [5,7,18,19,24].

From a surgical perspective, aneurysmectomy with interposition of a tube graft represented the most frequently performed procedure in both groups. Consistent with previous reports [5,6,19,24], operative duration and intraoperative blood loss did not differ significantly between the groups, suggesting that symptomatic presentation alone does not necessarily increase technical complexity during open surgical repair.

Despite comparable intraoperative parameters, hospital stay was significantly longer in the SAAA group, likely reflecting both the higher postoperative complications, as well as the need for preoperative hospitalization for diagnostic evaluation and hemodynamic stabilization.

Thirty-day mortality was slightly higher in the SAAA group, although the difference did not reach statistical significance. This observation indicated that OSR of symptomatic non-ruptured AAA can be performed with acceptable early survival in specialized centers, which is consistent with findings from previous studies [6,7,16–19,24]. Nevertheless, overall postoperative complications occurred significantly more frequently in SAAA patients, in agreement with reports by Soden et al. [5], Mroczek [18], and Chandra et al. [6]. Other studies [18] suggested better outcomes with EVAR overall, although these differences likely reflect varying institutional experience.

In our cohort, cardiac complications were more frequent among patients with SAAA, consistent with the increased cardiovascular stress associated with symptomatic disease [18,19]. In contrast, pulmonary and local complications did not differ significantly between the groups.

Importantly, the incidence of AKI did not differ significantly between SAAA and AsAAA groups. However, postoperative AKI was strongly associated with preoperative CKD (OR 10.5, 95% CI 4.0–27.5) and preoperative anemia (OR 9.5, 95% CI 3.5-22.5). These findings indicate that baseline renal dysfunction and reduced oxygen-carrying capacity represent major vulnerabilities in patients undergoing open AAA repair. These results are consistent with several studies demonstrating that preoperative CKD and reduced eGFR (< 60 mL/min/1.73 m^2) are independent predictors of postoperative AKI, regardless of repair technique used [20–22,25–27].

Conclusion

In this retrospective cohort study, symptomatic non-ruptured aortic aneurysms were significantly larger and associated with higher postoperative complication rates and prolonged hospitalization compared with asymptomatic aneurysms. However, 30-day mortality and the incidence of acute kidney injury did not differ significantly between the two groups. Preoperative chronic kidney disease and anemia emerged as the strongest predictors of postoperative acute kidney injury, regardless of symptomatic status. These findings emphasize the critical importance of preoperative risk stratification and optimization of renal function. Overall, open surgical repair of symptomatic non-ruptured abdominal aortic aneurysm can be performed with acceptable outcomes in high-volume centers, particularly when supported by careful patient selection and comprehensive perioperative management strategies.

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REVIEW ARTICLES
PREGLEDNI ČLANCI

PREOPERATIVE CONSIDERATIONS AND MOST COMMON NON-OBSTETRIC SURGICAL CONDITIONS IN PREGNANCY

PREOPERATIVNA RAZMATRANJA I NAJČEŠĆA NEAKUŠERSKA HIRURŠKA STANJA U TRUDNOĆI

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Abstract

Introduction. During pregnancy, approximately 1-2% of patients undergo non-obstetric surgical interventions. Pregnant women are considered at increased risk in the perioperative period, due to anatomical and physiological changes that occur during gravidity. **Anatomical and physiological changes.** Changes in the respiratory tract are especially pronounced towards the end of pregnancy. These changes include swelling of the oropharyngeal tissues and reduced caliber of the glottis, which can lead to difficulty during ventilation and intubation. **Perioperative anesthesiological considerations.** Carefully titrating anesthetics is essential, as drug requirements are usually reduced during pregnancy. **Medications and toxicity.** Drugs administered during pregnancy may have a harmful effect on the fetus depending on dosage, method of administration and time of exposure. Despite years of animal experiments and observational studies in humans, no anesthetic has been shown to be clearly dangerous to the human fetus. **Fetal monitoring.** Accurate interpretation of fetal heart rate patterns and understanding of the effects of anesthetics enable effective monitoring of fetal well-being and informed decision-making regarding intraoperative care for the safety of both mother and fetus. **Non-obstetric surgical conditions.** Appendicitis and cholecystitis are the two most common surgical conditions that require treatment during pregnancy. Other more common conditions are chronic inflammatory bowel diseases and pancreatitis. Traumatic injuries of pregnant patients are a special topic. **Conclusion.** Comprehensive preoperative preparation should performed before every surgical intervention. Pregnant women should never be denied an emergency indicated surgical procedure, regardless of the current trimester of pregnancy.

Key words: Pregnancy; Periperative Care; Abdominal Surgical Procedures; Appendicitis; Cholecystitis; Risk Factors; Fetal Monitoring; Pregnancy Complications; Airway Management; Anesthetics

Sažetak

Uvod. Oko 1-2% trudnica tokom perioda trudnoće podvrgne se neopstetričkoj hirurgiji. Trudnice se smatraju grupom sa većim perioperativnim rizikom zbog fizioloških i anatomskih promena koje se razvijaju u trudnoći. **Anatomske i fiziološke specifičnosti graviditeta.** Promene disajnog puta su posebno izražene pred kraj trudnoće. Ove promene uključuju otok orofaringealnih tkiva i smanjen kalibar glotisnog otvora, što može dovesti do poteškoća tokom ventilacije i intubacije. **Perioperativna anesteziološka razmatranja.** Neophodno je pažljivo titrirati anestetike, jer su potrebe za lekovima tokom trudnoće obično smanjene. **Medikamenti i toksičnost.** Lekovi dati tokom trudnoće mogu imati štetan efekat na fetus u zavisnosti od doze, načina primene i vremena izloženosti. Uprkos godinama eksperimenata na životinjama i opservacionih studija na ljudima, nijedan anestetik nije pokazan kao jasno toksičan za ljudski fetus. **Fetalni monitoring.** Tačno tumačenje obrazaca fetalne srčane frekvencije i razumevanje uticaja anestetika omogućavaju efikasno praćenje dobrobiti fetusa i donošenje informisanih odluka o intraoperativnom zbrinjavanju radi bezbednosti i majke i fetusa. **Neopstetrička hirurška stanja.** Apendicitis i holecistitis jesu dva najčešća hirurška abdominalna, neginekološka oboljenja koja zahtevaju lečenje u trudnoći. Ostala učestalija stanja jesu hronične inflamatorne bolesti creva i pankreatitis. Poseban entitet jesu traumatske povrede gravidnih bolesnica. **Zaključak.** Neophodno je sprovesti sveobuhvatnu preoperativnu pripremu trudnice pred planirani operativni zahvat. Trudnici se nikada ne sme uskratiti hitan indikovani operativni zahvat, bez obzira na aktuelni trimestar trudnoće.

Ključne reči: trudnoća; perioperativna nega; abdominalne hirurške procedure; apendicitis; holecistitis; faktori rizika; fetalni monitoring; komplikacije u trudnoći; zbrinjavanje disajnog puta; anestezija

Introduction

About 1-2% of pregnant women undergo non-obstetric surgery during pregnancy [1]. Diagnosing and managing non-obstetric abdominal pathologies during pregnancy represents a clinical challenge for both obstetricians and anesthesiologists. During anesthetic and perioperative surgical care of pregnant

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Abbreviations

FDA – The Food and Drug Administration
DNA – deoxyribonucleic acid
NSAID – non-steroidal anti-inflammatory drugs
MRI – magnetic resonance imaging

patients, strict patient selection and careful timing are key factors when deciding to perform non-obstetric surgical procedures [2]. Pregnant women are considered a group with higher perioperative risk due to physiological and anatomical changes that develop during pregnancy. These changes, driven by hormonal factors and mechanical effects of the enlarged uterus, have important implications for both surgeons and anesthesiologists [3]. Nevertheless, an urgently indicated operation must never be withheld from a pregnant patient, regardless of the current trimester [4]. Appendicitis, cholecystitis, ovarian torsion, maternal malignancies, and traumatic injuries are the most common indications for surgical intervention during pregnancy [5]. The most frequent non-obstetric procedures performed in pregnancy are appendectomy (44%) and cholecystectomy (22.3%) [3].

Anatomical and physiological specificities of pregnancy

The primary physiological changes that occur during pregnancy are influenced by pregnancy hormones. These changes are crucial to ensure adequate oxygen and nutrient delivery to the fetus [6].

Pregnant women exhibit changes in pain perception and pain threshold, reduced anesthetic requirements, and physiologically increased activity of the sympathetic nervous system. The minimum alveolar concentration for volatile anesthetics decreases by 28% at 8-12 weeks of gestation, reaches 40% of the non-pregnant value as pregnancy progresses, and returns to baseline by day three postpartum [7].

Airway changes may appear halfway through the second trimester and are particularly pronounced near the end of pregnancy. These changes include edema of oropharyngeal tissues and reduced glottic aperture, which may lead to difficulty with ventilation and intubation [2]. Due to cranial displacement of the diaphragm by the gravid uterus, the transverse diameter of the chest increases and functional residual capacity decreases by 20%. Minute ventilation increases by 50%. The combination of increased minute ventilation and reduced functional residual capacity explains the rapid uptake of volatile anesthetics [8]. Increased maternal resting metabolism and the increased metabolic demands of the fetoplacental unit raise oxygen consumption by 60% [9]. Reduced functional residual capacity along with increased oxygen demand underlies rapid oxygen desaturation that can occur in pregnant women in the event of apnea or airway obstruction.

During pregnancy, cardiac output increases by 50%, with a consequent rise in heart rate (by 10-20/min) and stroke volume (30–40%). Accordingly, induction of anesthesia with intravenous agents is faster [8]. This increase begins early in pregnancy. As cardiac output rises, systemic vascular resistance and pulmonary vascular resistance decrease simultaneously[10].

Regarding intraoperative positioning, after 18–20 weeks of gestation, pregnant patients should be positioned with a 15° left lateral tilt during surgery. This reduces aortocaval compression and mitigates the risk of supine hypotensive syndrome, which can occur due to pressure on both venae cavae when the patient lies flat on her back [11]. Because fetal perfusion is determined by maternal blood pressure, avoiding maternal hypotension is essential. In addition to preventing hypotension, maintaining maternal blood oxygenation is crucial in avoiding fetal hypoxemia during general anesthesia [8]. During surgical procedures in pregnant women, precautionary measures are aimed at preventing four key risks: hypotension, hypoxemia, hypovolemia, and hypothermia [12].

Aspiration of gastric contents is rare, with an incidence of 2:10,000, but recognizing risk factors (obesity and a known difficult airway) and adequate preparation (preoperative fasting and gastric decompression in selected cases) are imperative for preventing aspiration [13]. The gravid uterus increases intragastric pressure and reduces the protective effect of the diaphragm on the lower esophageal sphincter. Gastroesophageal reflux and regurgitation are more common in pregnant women than in the general population [8].

Because pregnancy leads to a procoagulant state, perioperative venous thrombosis prophylaxis should be considered [14]. For abdominopelvic procedures lasting more than 45 minutes, the risk of thromboembolic complications is moderate. Unfractionated and low-molecular-weight heparin are considered safe in pregnancy [15].

In Rh-negative mothers who are expected to deliver an Rh-positive child, there is an increased risk of hemolytic anemia. Preventively, in such cases, the mother should receive anti-D immunoglobulin [16].

Perioperative anesthetic considerations for non-obstetric surgery in pregnancy

The risks of surgery during pregnancy are determined by numerous factors, including physiological changes, potential adverse effects of anesthetic agents, gestational age, the type, duration, and location of the

surgical pathology, the anesthetic technique, and the patient's overall condition. Each pregnant patient should be assessed by an anesthesiologist to evaluate general status, potential comorbidities, fetal viability, and gestational age. An individualized plan should be developed to ensure maternal and fetal safety, control teratogenic risk, avoid intrauterine fetal asphyxia, and prevent preterm labor [17]. Despite careful management, patients exposed to surgery and anesthesia during pregnancy may still develop serious complications, including pneumonia, sepsis, venous thromboembolism, and even death, as well as fetal loss, preterm delivery, and low birth-weight neonates [7].

Pregnant patients requiring surgery should undergo preoperative preparation in a manner similar to non-pregnant patients. This comprehensive approach ensures the safety and well-being of both mother and fetus [11]. Mallampati scores III and IV have been described in 12% of women in the first trimester. This proportion rises to 20% in the second trimester, which is considered the preferred time for non-urgent procedures. This emphasizes the importance of careful airway assessment and preparation [18]. The incidence of failed intubation in obstetrics is 1:390-443 and is higher than in non-obstetric patients [13]. In addition to the expected risk of difficult intubation, the anesthesiologist should also pay special attention to extubation and subsequent postoperative care. Failed intubation in obstetrics affects both mother and fetus [8]. According to one study, a higher number of neonatal intensive care unit admissions was reported among newborns whose mothers had difficult intubation [19]. A routine "head-up" position during induction of general anesthesia is recommended, as it facilitates airway manipulation and laryngoscopy, particularly in pregnant women with enlarged breasts. To prevent desaturation during induction, the following are recommended: preoxygenation with a tightly fitted face mask for at least three minutes and achieving end-tidal oxygen of 90%; mask ventilation prior to intubation (with a maximum inspiratory pressure of 20 cmH_2O); and passive oxygenation during apnea via nasal cannula at 5-15 L/min [8]. An increasing number of studies suggest that videolaryngoscopy should be the first-line method for securing the airway [20]. Cricoid pressure should not be applied if it impairs airway management and intubation on the first laryngoscopy attempt. If the first intubation attempt fails, mask ventilation and oxygenation should be resumed. The next (second) attempt should be performed by the most experienced available anesthesiologist, using a different laryngoscope if available. If cricoid pressure was used during the first attempt, the second attempt should be without cricoid compression. It is recommended to limit the maximum number of intubation attempts to two. A third attempt, in special circumstances, should be performed by the most senior anesthesiologist. If failed intubation is declared, the priority is to ensure oxygenation via a face mask or second-generation supraglottic airway devices [8].

After failed intubation and the decision to proceed with the surgical intervention, anesthesia should be maintained as safely as possible, ensuring adequate ventilation and appropriate anesthetic depth. Controlled ventilation, non-depolarizing neuromuscular blockers, second-generation supraglottic airway devices, and inhalational anesthetics are preferred. A gastric tube should be passed through the laryngeal mask to decompress the stomach. If the surgical procedure is abandoned due to failed intubation, the plan for further safe management should be formulated by the team. Regional anesthesia techniques and awake tracheal intubation should be considered. Awake tracheal intubation may be performed using a flexible bronchoscope, rigid direct or indirect laryngoscopy, or tracheostomy. Regardless of the final airway technique and type of anesthesia, the occurrence of difficult and/or failed intubation should be documented in the patient's medical records, particularly because the patient may require general anesthesia later in life [8].

The incidence of non-obstetric surgery during pregnancy is 0.48%, with most procedures performed in the second trimester (44%) and under general anesthesia (81%) [21]. Regional anesthesia offers several advantages in pregnant patients. It usually involves lower drug exposure, a lower risk of teratogenicity, especially in the first trimester, and reduces interference with fetal monitoring later in pregnancy. Regional techniques often provide better postoperative analgesia, facilitate early mobilization, and reduce the risk of thromboembolism [11]. General anesthesia was long considered the anesthesia of choice for vaginal delivery and cesarean section in obstetrics [8]. Although mortality associated with general anesthesia in obstetrics declined by 60% in the period 1991-2002 compared with 1979-1990, literature still reports maternal deaths associated with difficult intubation [22,23]. When surgery is performed under general anesthesia, a higher frequency of low birth-weight neonates has been observed, and the rate of preterm delivery is higher for procedures performed in the third trimester compared with the other trimesters [21].

Anesthetic agents should be carefully titrated because drug requirements during pregnancy are generally reduced for both volatile and intravenous anesthetics. This ensures that maternal physiological changes are properly managed and that anesthesia remains effective without unnecessary risk to the mother or fetus [24]. Pregnant women are also more sensitive to neu-

romuscular blockers. Although the dose of succinylcholine is usually not reduced, neuromuscular blockade may be mildly prolonged due to decreased pseudocholinesterase activity. These findings highlight the importance of careful titration and monitoring of anesthetic agents for optimal anesthetic management in pregnant patients undergoing surgery [10]. Ketamine has been shown to induce uterine contractions in early pregnancy similarly to ergometrine, but this effect is not present in late pregnancy. Therefore, ketamine's excellent analgesic properties can be safely utilized in late pregnancy. Volatile anesthetics such as halothane, sevoflurane, desflurane, and isoflurane have been shown to inhibit uterine contractility, potentially contributing to uterine relaxation and reducing the frequency of preterm labor [5].

When appropriate, analgesic modalities such as continuous peripheral or neuraxial blocks though IV infusions are optimal for postoperative pain control. Adequate postoperative analgesia is essential, as studies have shown that pain can increase the risk of preterm labor. By effectively controlling postoperative pain, clinicians can reduce this risk and improve outcomes for both mother and fetus [11]. After surgery, early mobilization is recommended to reduce the risk of deep vein thrombosis [25].

Medications and Toxicity

In the first 15 days of pregnancy, the "all-or-nothing" phenomenon occurs: either fetal loss occurs, or the fetus remains unaffected. During organogenesis (from day 15 to day 56), structural anomalies develop, whereas after this period functional abnormalities may occur, depending on the specifics of the case [17]. Teratogenesis may manifest as structural anomalies (e.g., growth restriction or congenital malformation) or as functional, behavioral, or cognitive delays [7]. The Food and Drug Administration (FDA) introduced fetal risk categories for medications, from Category A (safest) to Category X (known danger) [26]. Drugs administered during pregnancy may harm the fetus depending on dosage, route of administration, and timing of exposure. Despite years of animal experiments and observational human studies, no anesthetic has been shown to be clearly toxic to the human fetus [1]. Anesthetic agents such as induction agents, inhalational and intravenous agents, muscle relaxants, local anesthetics, benzodiazepines, and opioids, when used under normal clinical conditions, have been shown to be safe and nonteratogenic [17]. Nitrous oxide inhibits methionine synthase activity and may affect deoxyribonucleic acid (DNA) synthesis in the developing fetus, and can be teratogenic during the peak of organogenesis in rodents. Regarding antibiotics, cephalosporins, penicillins, and macrolides can be used safely. Amoxicillin-clavulanate should be avoided due to an increased risk of necrotizing enterocolitis. Although considered relatively safe, the main adverse effects of aminoglycosides are ototoxicity and nephrotoxicity in both the mother and fetus [27]. Anticholinesterases may increase uterine tone during pregnancy, so slow administration is recommended [17]. Sugammadex may encapsulate progesterone and reduce progesterone levels in pharmacologic simulation studies [7].

Benzodiazepine use is associated with anorectal anomalies and additional congenital defects. Opioids readily cross the fetoplacental barrier, and in-utero exposure may lead to fetal-neonatal respiratory distress syndrome, a higher incidence of neonatal hospitalizations, and the development of behavioral developmental disorders. Guidelines recommend that opioids and paracetamol (acetaminophen) may be used to treat mild to moderate pain during pregnancy. Preference is given to paracetamol, especially as it is considered safe in pregnancy and has no known teratogenic effects. However, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided due to potential fetal risks [10]. NSAIDs should be avoided, especially in advanced gestation, because of the risk of oligohydramnios, premature closure of the ductus arteriosus, and necrotizing enterocolitis. Additionally, they can inhibit uterine contractions, making them unsuitable for pain treatment in pregnancy, particularly in later stages [11]. A prospective Norwegian cohort study on NSAID exposure during pregnancy and the risk of selected congenital malformations showed that NSAID exposure during the first 12 weeks of gestation does not appear to be associated with an increased risk of selected congenital malformations [28].

Antenatal corticosteroid administration should be considered in mothers with a viable fetus (23-24 gestational weeks) up to 33 weeks plus six days of gestation if there is an increased risk of preterm birth within the next 1-7 days. Perinatal morbidity is significantly lower in children born before 34 gestational weeks if antenatal corticosteroids were administered. When deciding on corticosteroid use, their adverse effects should be considered, such as the risk of neonatal hypoglycemia and a potential impact on neurological development [29].

Fetal monitoring

The decision to use fetal monitoring during surgery in pregnant patients should be individualized, taking into account gestational age, maternal status, the type and duration of surgery, and fetal well-being.

Accurate interpretation of fetal heart rate patterns and knowledge of anesthetic effects enable effective assessment of fetal well-being and informed intraoperative management decisions to ensure maternal and fetal safety [1]. If the fetus is considered pre-viable, it may be sufficient to confirm the fetal heart rate by Doppler before and after the procedure. For viable fetuses, simultaneous electronic monitoring of fetal heart rate and uterine contractions should be performed before and after the procedure to assess fetal well-being and the absence of contractions. Continuous intraoperative fetal heart rate monitoring is advised only when interrupting the non-gynecologic surgical procedure is possible if the need for emergency delivery arises, and when an obstetrician capable of performing an emergency cesarean section is present in the operating room in case of pathological fetal heart rate tracings [30]. Fetal heart rate monitoring is feasible from approximately 18-22 weeks of gestation. However, from around 25 weeks, heart rate variability becomes easier to recognize, providing important information about fetal well-being [11]. In addition, regardless of gestational age, fetal heart rate monitoring should be documented before and after the surgical procedure. It is also important to emphasize that general anesthetics cross the placenta and may cause absent fetal heart rate variability, highlighting the importance of careful monitoring and timely intervention to ensure maternal and fetal safety during surgery [4]. It should also be kept in mind that certain anesthetics can cause changes in fetal heart rate monitoring tracings, such as opioids, beta-blockers, atropine, and magnesium sulfate. Careful consideration of these factors is necessary for maternal and fetal safety during surgical procedures [10].

Non-obstetric surgical conditions

Intra-abdominal pathological processes pose a particular challenge in pregnant patients, most notably in respect to balancing risk factors and potential benefits of surgery [12]. Appendicitis and cholecystitis are the two most common abdominal, non-gynecologic surgical diseases requiring treatment during pregnancy. Other more frequent conditions include chronic inflammatory bowel disease and pancreatitis. Traumatic injuries in pregnant patients represent a separate topic.

Initial diagnosis is often difficult due to the non-specific nature of symptoms such as abdominal pain, bloating, and nausea [31]. Additionally, the gravid uterus displaces intra-abdominal organs, which can complicate clinical examination. Traditionally, the beginning of the second trimester is considered the most suitable period for performing surgery for several reasons: the risk of preterm birth is thought to be lowest, and the gravid uterus is believed not to significantly impair surgical visualization of abdominal structures [32]. Regarding radiologic diagnostics, ultrasound and magnetic resonance imaging (without gadolinium) are first-line modalities because they avoid radiation exposure to the mother and fetus. If imaging that produces ionizing radiation is necessary, consultation with a radiologist is advised to ensure adequate diagnostics using minimal radiation doses [33].

Appendicitis occurs in 0.05-0.15% of pregnancies [34] and most commonly presents in the second trimester [35]. Diagnosis is not always straightforward. Patients most often report pain in the right lower quadrant, although pain may be present in any abdominal region [36]. The gravid uterus can often displace the appendix. In laboratory testing, appendicitis is most commonly associated with hyperbilirubinemia, leukocytosis, an elevated neutrophil-to-lymphocyte ratio, and an elevated platelet-to-lymphocyte ratio [37]. The initial imaging modality is ultrasound; however, reported sensitivity in pregnant women ranges from 28-100% and specificity from 33-92%, with declining sensitivity in later trimesters [32]. Computed tomography and magnetic resonance imaging demonstrate sensitivity and specificity of nearly 100% [38]. Appendicitis during pregnancy is associated with preterm birth, intra-amniotic infection, and intrauterine fetal demise. Current recommendations indicate that in acute appendicitis, surgical appendectomy is the treatment of choice compared with conservative management. In addition, appendectomy is associated with a lower need for cesarean delivery, fewer re-hospitalizations of pregnant/postpartum patients, and a lower incidence of maternal sepsis [39]. Regarding surgical technique, laparoscopic appendectomy is recommended over open appendectomy when the uterine fundus is below the level of the umbilicus. In later stages of pregnancy, the enlarged uterus may affect port placement as well as the available infra-abdominal space required for safe laparoscopy [12].

Cholecystitis occurs somewhat less frequently, in 0.01-0.06% of cases. Spontaneous perforation occurs in approximately 2-10% of patients with acute cholecystitis and often presents with nonspecific symptoms, which complicates timely diagnosis [40]. Symptoms and signs in pregnant patients are similar to those in the general population. For example, intermittent postprandial pain in the right upper quadrant and/or epigastrium suggests biliary colic. In laboratory testing, elevated total and direct bilirubin levels as well as gamma-glutamyl transferase suggest biliary obstruction [41]. Ultrasound is the imaging modality of choice, with nearly 100% sensitivity for gallstones and 95% sensitiv-

ity for cholecystitis [42]. In unclear cases, abdominal magnetic resonance imaging (MRI) should be performed [32]. Laparoscopic cholecystectomy is recommended over conservative treatment of biliary disease during pregnancy; therefore, in acute cholecystitis, laparoscopic cholecystectomy is the treatment of choice. However, in biliary colic during the third trimester, both conservative and operative management should be considered. Reported benefits of laparoscopic cholecystectomy include lower incidence of cesarean delivery, delivery during hospitalization, neonatal death, neonatal intensive care admission, pregnancy loss, and maternal re-hospitalization. Reported risk factors associated with laparoscopic cholecystectomy include sepsis, preeclampsia, and postoperative bile leakage from the operative field [12]. According to some studies, preterm birth and eclampsia are more frequent in patients operated in the last trimester compared with those operated in the first three postpartum months [43]. In pregnant patients with symptomatic choledocholithiasis, endoscopic retrograde cholangiopancreatography is recommended over conventional surgical exploration of the bile ducts [12].

In patients with inflammatory bowel disease, emergency surgical conditions may occur due to bowel perforation or persistent bowel obstruction. Indications for emergency surgery are the same in pregnant and non-pregnant patients. Open surgery is the approach of choice [12]. The use of mesalamine, sulfasalazine, steroids, thiopurines, and biologics is relatively safe in pregnancy, with the need for additional consideration depending on trimester, the patient's overall status, and incomplete data in the available literature. Inflammatory bowel disease is associated with prematurity, low birth weight, congenital anomalies, and a higher incidence of cesarean delivery [44].

Pancreatitis occurs in pregnant women at a similar incidence as in the general population [33]. Pancreatitis develops in 0-29% of cases in the first trimester, 4.8-63.6% in the second, and 27.3-95.2% in the third trimester [45,46]. The most common causes during pregnancy are biliary calculi and hypertriglyceridemia. Maternal complications of pancreatitis include multi-organ dysfunction, acute respiratory failure, venous thromboembolism, disseminated intravascular coagulation, preeclampsia, postpartum hemorrhage, and death (0-5.1%) [46]. Typical symptoms include severe epigastric pain radiating to the back, nausea, and vomiting. Elevation of amylase and lipase to three times the upper reference limit, along with appropriate clinical symptoms and imaging findings, is sufficient to establish the diagnosis of pancreatitis [47]. Initial treatment includes fluid resuscitation, correction of electrolyte imbalance, multimodal analgesia, and antiemetic therapy. Although parenteral nutrition is often initiated, early enteral nutrition should be emphasized [45]. More invasive treatment modalities include endoscopic retrograde cholangiopancreatography and surgical cholecystectomy [32].

Traumatic injuries during pregnancy are the leading cause of non-obstetric maternal mortality, with nearly 20% of maternal deaths occurring as a direct consequence of injury. Non-fatal injuries most commonly occur as a result of traffic accidents or domestic/partner violence [48]. Management of pregnant trauma patients requires consideration of anatomical and physiological changes, potential exposure to ionizing radiation or teratogenic medications, the need to assess fetal viability, and other pregnancy-specific issues discussed above. During initial management, it is advised that every woman of reproductive age be considered pregnant until proven otherwise, since nearly 3% of women hospitalized after traumatic injuries are pregnant, and among them 11% are incidental pregnancies. When securing the airway, the previously described pregnancy-specific airway considerations should be taken into account. In addition, due to delayed gastric emptying, a pregnant patient should be considered to have a "full stomach" up to 24 hours after the last meal. For vascular access in all severely injured patients, placement of two peripheral IV lines (14–16G) is recommended to enable rapid crystalloid resuscitation, correction of hypovolemia, and administration of blood and blood products as indicated. Vasopressors can significantly reduce placental perfusion; therefore, their use should be delayed if there is a positive response to fluid administration and hypotension can be corrected with volume resuscitation. Ultimately, treatment of the injured mother should take priority over any intervention aimed at fetal benefit [49].

Conclusion

Although the second trimester is considered the safest time for surgical procedures, pregnant women should never be denied an emergency indicated surgical procedure, regardless of the current trimester of pregnancy. Appendicitis and cholecystitis are the two most common abdominal, non-gynecologic surgical conditions requiring treatment during pregnancy. Comprehensive preoperative preparation should be performed before every surgical intervention, with special emphasis on preoperative airway assessment and adequate preparation for difficult intubation. When it comes to the use of anesthetics, most drugs used in general anesthesia are considered safe, both for the pregnant patient and the fetus.

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SEMINAR FOR PHYSICIANS
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ARTIFICIAL INTELLIGENCE IN *IN VITRO* FERTILIZATION: CURRENT APPLICATIONS, LIMITATIONS AND FUTURE DIRECTIONS

VEŠTAČKA INTELIGENCIJA U PROCESU VANTELESNE OPLODNJE: PRIMENE, OGRANIČENJA I BUDUĆNOST

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Abstract

Introduction. Infertility represents a major global health challenge with profound medical, psychological, and social consequences. Despite substantial advances in assisted reproductive techniques, the success rates of *in vitro* fertilization remain limited, largely due to subjectivity in embryo selection and variability in ovarian stimulation management. **Application of artificial intelligence in embryo selection**. Artificial intelligence systems enable the analysis of large and complex datasets, including morphological and morphokinetic embryo characteristics derived from static imaging and continuous developmental monitoring. These approaches enhance the standardization of embryo quality assessment and reduce interobserver variability; however, their performance remains constrained by the quality of training data and the incomplete representation of biological determinants of implantation. **Role of artificial intelligence in ovarian stimulation management**. Algorithms integrating clinical, hormonal, and ultrasonographic parameters facilitate individualized gonadotropin dosing, more accurate determination of final oocyte maturation timing, and reduction of ovarian hyperstimulation risk. Existing studies demonstrate a high level of concordance between algorithm-based recommendations and expert clinical decision-making. **Future directions**. Further advancements are anticipated through the development of multimodal models integrating morphological, clinical, and genetic data, alongside the implementation of explainable systems to enhance transparency and clinical trust. **Conclusion**. Currently, artificial intelligence serves primarily as a decision-support tool rather than a substitute for clinical expertise. Its routine clinical implementation requires robust prospective validation and regulatory approval.

Key words: Artificial Intelligence; Fertilization in Vitro; Reproductive Techniques, Assisted; Embryo Transfer; Infertility; Ovulation Induction; Machine Learning; Decision Support Systems, Clinical

Sažetak

Uvod. Neplodnost predstavlja značajan globalni zdravstveni problem sa dalekosežnim medicinskim, psihološkim i društvenim posledicama. I pored napretka u metodama asistirane reprodukcije, uspešnost postupaka oplodnje van tela i dalje je ograničena, naročito zbog subjektivnosti u selekciji embriona i vođenju ovarijalne stimulacije. **Primena veštačke inteligencije u selekciji embriona**. Savremeni sistemi veštačke inteligencije omogućavaju analizu velikih skupova podataka, uključujući morfološke i morfokinetičke karakteristike embriona dobijene statičkim snimanjem i kontinuiranim praćenjem razvoja. Ovi sistemi doprinose standardizaciji procene kvaliteta embriona i smanjenju varijabilnosti među embriolozima, ali su i dalje ograničeni kvalitetom ulaznih podataka i nedovoljnom obuhvaćenošću svih bioloških faktora relevantnih za implantaciju. **Uloga veštačke inteligencije u vođenju ovarijalne stimulacije.** Algoritmi zasnovani na kliničkim, hormonskim i ultrazvučnim parametrima omogućavaju individualizaciju doziranja gonadotropina, preciznije određivanje trenutka indukcije završnog sazrevanja oocita i smanjenje rizika od sindroma ovarijalne hiperstimulacije. Studije pokazuju visok stepen saglasnosti ovih sistema sa kliničkim odlukama iskusnih lekara. **Budući pravci.** Dalji razvoj ide ka multimodalnim modelima koji integrišu morfološke, kliničke i genetske podatke, kao i ka objašnjivim modelima koji bi povećali kliničko poverenje. **Zaključak**. Veštačka inteligencija trenutno predstavlja alat za podršku odlučivanju, a ne zamenu za kliničko iskustvo. Njena rutinska primena zahteva dodatne prospektivne studije i regulatornu validaciju.

Ključne reči: veštačka inteligencija; vantelesna oplodnja; potpomognute reproduktivne tehnike; transfer embriona; neplodnost; stimulacija jajnika; mašinsko učenje; sistemi za kliničku podršku odlučivanju

Introduction

Infertility affects approximately 15% of couples worldwide and imposes substantial psychological, social, and economic burdens [1]. When natural conception is unsuccessful, assisted reproductive technologies (ART) – particularly *in vitro* fertilization (IVF) – are commonly employed. IVF encompasses controlled ovarian stimulation, oocyte retrieval, laboratory fertilization, embryo culture, and embryo transfer [2,3].

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Abbreviations

AFC	– antral follicle count
AI	– artificial intelligence
AMH	– anti-Müllerian hormone
ART	– assisted reproductive technologies
BMI	– body mass index
CNN	– convolutional neural network
DL	– deep learning
E2	– estradiol
FSH	– follicle-stimulating hormone
ICSI	– intracytoplasmic sperm injection
ILETIA	– individualized trigger-to-oocyte pickup interval estimation algorithm
IVF	– *in vitro* fertilization
ML	– machine learning
OHSS	– ovarian hyperstimulation syndrome
P4	– progesterone
PGT-A	– preimplantation genetic testing for aneuploidies
XAI	– explainable artificial intelligence

Despite continuous technological advancements, clinical outcomes – including pregnancy, implantation, and live-birth rates per embryo transfer – remain modest (typically < 30%) and are influenced by factors such as maternal age, ovarian response, embryo quality, and endometrial receptivity [3,4].

Conventional embryo selection relies on morphological assessment at predefined time points, with embryologists evaluating blastomere symmetry, fragmentation, and blastocyst morphology to guide transfer decisions [4,5]. However, this approach is inherently subjective and prone to interobserver variability, and morphologically normal embryos may still harbor chromosomal or functional abnormalities that comprise implantation potential [4,5]. Time-lapse incubation systems provide continuous morphokinetic data – such as cleavage timing, compaction, and blastulation – while maintaining stable culture conditions. Nevertheless, interpretation of these data largely remains dependent on human judgment [5,6].

Against this backdrop, artificial intelligence (AI), including machine learning (ML) and deep learning (DL), has emerged as a powerful tool for analyzing large, heterogeneous datasets encompassing imaging, time-lapse recordings, hormonal profiles, ultrasonographic parameters, and clinical variables [2,7]. AI facilitates the identification of complex patterns beyond human perception, offering the potential to standardize embryo assessment and enable personalized decision-making through the IVF process. Several studies have demonstrated improved predictive performance of AI models compared to conventional morphological evaluation in selected datasets [4]. The clinical relevance of IVF outcomes at our institution has previously been documented, providing a baseline for longitudinal outcome assessment [8].

AI in embryo selection

AI-based embryo assessment models range from traditional ML classifiers to DL architectures, particularly convolutional neural networks (CNNs), trained on static images and time-lapse sequences. Deep learning extracts hierarchical visual features – including inner cell mass quality, trophectoderm structure, blastocoel expansion, and compaction dynamics – and integrates them with morphokinetic parameters to predict outcomes such as blastocyst development, implantation potential, and euploidy [4,5,9–11]. The incorporation of time-lapse imaging enhances temporal resolution, enabling the identification of kinetic markers (e.g., timing of early cleavages) that are not discernible from static images alone [5,11].

Key advantages of AI include improved reproducibility, scalability, and reduced variability associated with operator fatigue. Several retrospective and prospective studies suggest that AI-based classifiers may outperform conventional manual grading systems in predicting implantation and clinical pregnancy rates within specific cohorts [4,10]. Additionally, AI systems can systematically rank embryos and provide a valuable second opinion to support embryologist decision-making.

However, significant limitations persist. Many AI models rely on "ground truth" labels from embryologist assessments or clinical outcomes, rendering them susceptible to bias inherent in the training data. Consequently, AI systems may inadvertently perpetuate or amplify existing interobserver variability and clinic-specific practices rather than mitigate them [7]. Furthermore, image-based models fail to account for non-morphological determinants of implantation, such as endometrial receptivity, immunological factors, and sub-microscopic chromosomal abnormalities, unless such variables are explicitly incorporated [5]. Another major challenge is the limited interpretability of DL models, often characterized as "black boxes", which complicates clinical validation, regulatory approval, and user trust [5,7,12,13].

Given these constraints, current AI applications are best regarded as decision-support tools that enhance standardization and assist in embryo prioritization, while final clinical decisions remain under the responsibility of experienced embryologists [4,7].

AI in ovarian stimulation management

Ovarian stimulation protocols – including regimen selection, initial follicle-stimulating hormone (FSH) dosing, dose adjustments, timing of ovarian trigger, and prevention of ovarian hyperstimulation syndrome (OHSS) – significantly affect oocyte yield

and cycle safety. Traditionally guided by ultrasonographic findings, estradiol levels, and clinician expertise, this process is subject of considerable inter-physician variability.

AI models trained on large clinical datasets offer the potential to standardize and optimize these decisions. Relevant inputs variables include patient age, body mass index (BMI), anti-Müllerian hormone (AMH) levels, antral follicle count (AFC), baseline hormonal profiles, and dynamic follicular and estradiol measurements. For example, Letterie et al. developed a decision-support system trained on 2,603 IVF cycles (validated on 556 cycles), capable of recommending daily clinical actions - such as continuation or cessation of stimulation, dose adjustment, trigger timing, or cycle cancellation – with 92-96% concordance with clinician teams [14]. Similarly, prospective multicentre studies (e.g., Canon et al.) have demonstrated reduced cumulative FSH consumption without compromising the number of mature (MII) oocytes when AI-assisted recommendations are applied [15]. Real-world data further suggest improved stimulation efficiency without adverse effects on clinical outcomes [16].

Explainable AI (XAI) approaches applied to large datasets (e.g., 19,082 cycles in Hanassab et al.) have identified intermediate-sized follicles (13–18 mm) as strong predictors of mature oocytes and high-quality blastocysts, whereas a predominance of follicles > 18-mm is associated with progesterone elevation and suboptimal outcomes. These findings indicate that ovulation trigger timing should account for the overall follicular distribution rather than solely the leading follicle [17]. Emerging algorithms, such as ILETIA, aim to individualize the interval between ovulation trigger and oocyte retrieval, thereby optimizing MII oocyte yield through patient-specific timing adjustments [18].

The principle advantages of AI in this domain include improved standardization, individualized treatment strategies, reduced gonadotropin consumption, and optimized synchronization of follicular maturation [14–19]. Nonetheless, limitations parallel those observed in embryo selection, including dependence on retrospective datasets, limited external validation, potential bias inheritance, and a scarcity of randomized controlled trials with live birth as primary endpoint [2,14–19]. Additionally, challenges related to interpretability and regulatory approval continue to impede clinical adoption [12,13].

Future directions

Future developments in AI-assisted IVF are expected to focus on multimodal integration, combining embryo imaging/time-lapse, and morphokinetics with hormonal profiles (E2, P4, AMH), follicular dynamics, endometrial parameters, and genetic testing data (PGT-A) to improve prediction of implantation and live–birth outcomes [10,11]. Integration of imaging data with molecular and gene-expression profiles from the trophectoderm may enable simultaneous assessment of morphological, functional, and genetic embryo competence [20].

In parallel, robotic systems incorporating AI-guided image recognition are being developed assistance for micromanipulation such as intracytoplasmic sperm injection (ICSI). These systems demonstrate technical feasibility in experimental settings, enabling precise identification of cellular structures and stabilization of micromanipulation instruments; however, they remain investigational and lack regulatory approval for routine clinical use [21,22]. The concept of an integrated "AI embryologist assistant" – capable of monitoring ovarian stimulation, optimizing dosing strategies, ranking embryos, and supporting procedural tasks – holds considerable promise. However, its realization will require standardized datasets, robust explainability, clear regulatory frameworks, and high-quality randomized evidence demonstrating improvements in live-birth outcomes [14,23–25].

Conclusion

Artificial intelligence provides objective and reproducible support across critical stages of *in vitro* fertilization, particularly in embryo selection and ovarian stimulation management. At present, it serves to augment – rather than replace – clinical expertise. Key barriers to broader implementation include heterogeneity of training data, limited external validation, scarcity lack of randomized controlled trials with live birth as the primary endpoint, and challenges related to model interpretability. Future progress will depend on the development of multimodal, explainable artificial intelligence systems, rigorous clinical validation, and robust regulatory oversight to ensure patient safety and maintain clinical accountability.

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CASE REPORTS
PRIKAZI SLUČAJEVA

NON-SPECIFIC CLINICAL MANIFESTATION OF THE NODULAR TYPE OF CUTANEOUS MELANOMA

NESPECIFIČNA KLINIČKA MANIFESTACIJA NODULARNOG TIPA MELANOMA KOŽE

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Case report
Prikaz slučaja
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Abstract

Introduction. Nodular melanoma is an aggressive subtype of cutaneous melanoma characterized by rapid vertical growth, increased Breslow thickness at diagnosis, and early metastatic potential. Its atypical clinical presentation may mimic other skin tumors, leading to delayed recognition. **Case Report.** A 78-year-old patient presented with a giant, ulcerated, whitish, cauliflower-like tumor on the back, measuring 16 × 11 × 5 cm and attached by a narrow stalk. The initial clinical impression favored cutaneous squamous cell carcinoma. Radical excision with a 2.5 cm safety margin was performed. Histopathological examination confirmed nodular melanoma with Breslow thickness > 10 mm, Clark level IV, ulceration, satellitosis, and perivascular and intravascular invasion. Sentinel lymph node biopsy was recommended but declined. The patient did not return for follow-up, and the clinical outcome remains unknown. **Discussion.** This case highlights several diagnostic challenges. Giant nodular melanomas (> 10 cm) are rare, and minimal pigmentation may contribute to misdiagnosis. The tumor exhibited multiple high-risk features associated with nodal and distant metastasis. Early biopsy and accurate differential diagnosis are essential, as exophytic or atypical lesions may resemble non-melanocytic tumors. C**onclusion.** Atypical presentations of nodular melanoma require heightened clinical vigilance. Early recognition, appropriate surgical management, and adherence to staging protocols are essential for optimal outcomes.

Key words: Melanoma; Cutaneous Malignant Melanoma; Skin Neoplasms; Diagnosis, Differential; Signs and Symptoms; Biopsy

Sažetak

Uvod. Nodularni melanom predstavlja agresivan podtip kožnog melanoma, karakterisan brzim vertikalnim rastom, većom Breslou debljinom u trenutku dijagnoze i ranim metastatskim potencijalom. Njegova atipična klinička prezentacija može imitirati druge kožne tumore, što dovodi do odloženog prepoznavanja bolesti. **Prikaz slučaja.** Pacijent star 78 godina javio se sa velikim, ulcerisanim, beličastim, karfiolastim tumorom na leđima, dimenzija 16 × 11 × 5 cm, pričvršćenim uskom peteljkom. Inicijalni klinički utisak ukazivao je na planocelularni karcinom kože. Urađena je radikalna ekscizija sa bezbednosnom marginom od 2,5 cm. Histopatološka analiza potvrdila je nodularni melanom sa Breslou debljinom > 10 mm, Klark nivoom IV, ulceracijom, satelitima, kao i perivaskularnom i intravaskularnom invazijom. Preporučena je biopsija sentinel limfnog čvora, ali ju je pacijent odbio. Pacijent se nije odazvao na kontrole, pa njegov dalji klinički tok ostaje nepoznat. **Diskusija.** Ovaj slučaj ističe više dijagnostičkih izazova. Gigantski nodularni melanomi (> 10 cm) su retki, a oskudna pigmentacija može doprineti pogrešnoj dijagnozi. Tumor je pokazao više visokorizičnih karakteristika povezanih sa metastaziranjem u limfne čvorove i udaljene organe. Rana biopsija i precizna diferencijalna dijagnoza su od ključnog značaja, jer egzofitične ili atipične lezije mogu podsećati na neme-lanocitne tumore. **Zaključak.** Atipične i zavaravajuće prezentacije nodularnog melanoma zahtevaju povećanu kliničku budnost. Rano prepoznavanje, adekvatno hirurško lečenje i pridržavanje nacionalnih vodiča za lečenje bolesti od suštinske su važnosti za optimalne ishode.

Ključne reči: melanom; kutani maligni melanom; tumori kože; diferencijalna dijagnoza; znaci i simptomi; biopsija

Introduction

Melanoma is a malignant neoplasm arising from melanocytes, most commonly located in the skin, although it may also occur in other anatomical sites. In recent decades, it has become a significant global health concern due to its increasing incidence and high mortality rates [1,2]. According to the American Joint Committee on Cancer, melanoma is classified into several histopathological subtypes, including superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral lentiginous melano-

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Abbreviations
NM – nodular melanoma

ma, and unclassified variants [3]. Nodular melanoma (NM) accounts for approximately 10-15% of all cutaneous melanomas and represents the second most common subtype after superficial spreading melanoma. Clinically, NM typically presents as a rapidly enlarging, dome-shaped or nodular lesion, often deeply pigmented and most commonly located on sun-exposed areas, although it may also occur on covered regions. Compared with other melanoma subtypes, NM is associated with greater Breslow thickness at diagnosis, contributing to its more aggressive clinical course and poorer prognosis [4]. Even in its early stages, NM demonstrates a strong propensity for vertical growth and early metastatic dissemination to regional lymph nodes and distant organs [5]. Due to its rapid progression and occasionally atypical clinical presentation, nodular melanoma may be misdiagnosed as other cutaneous lesions, including squamous cell carcinoma, basal cell carcinoma, or benign proliferative conditions [6].

This report describes a case of giant nodular melanoma with an unusual clinical presentation, emphasizing the importance of maintaining high index of suspicion and performing timely histopathological evaluation of atypical skin lesions.

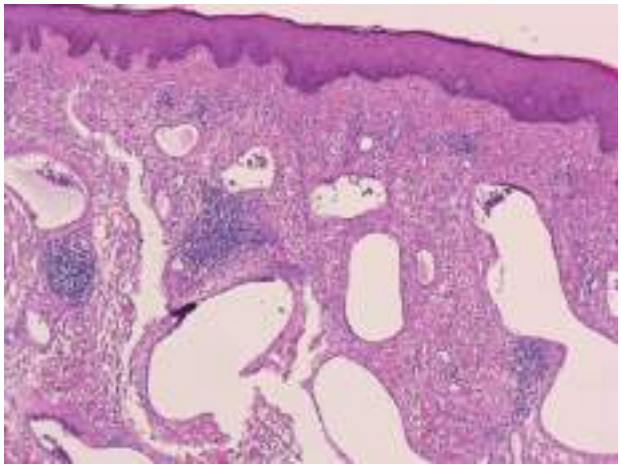

Figure 1. Clinical presentation of the nodular melanoma

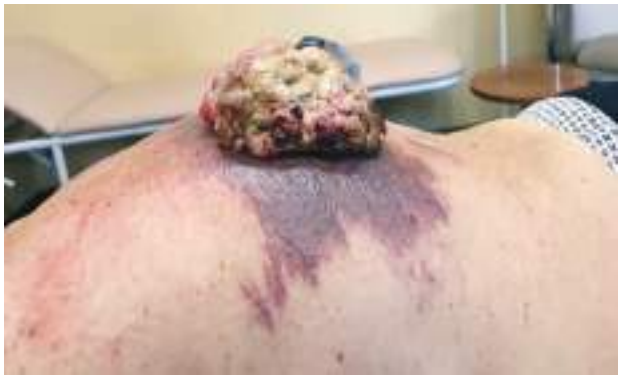

Figure 2. *Ex tempore* biopsy peritumorous tissue – without tumor cells

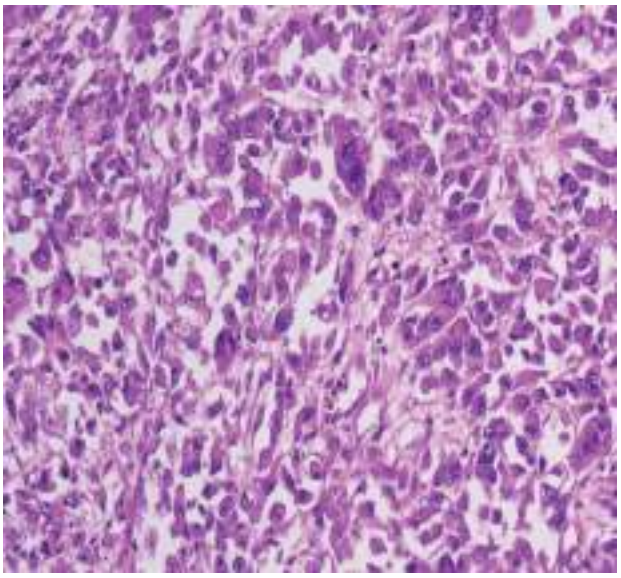

Figure 3. Bissare cells

Case Report

A 78-year-old patient presented with an ulcerated, predominantly whitish, cauliflower-like tumor located on the back, measuring 16 × 11 × 5 cm and attached by a narrow stalk. Based on its macroscopic appearance, the initial working diagnosis was cutaneous squamous cell carcinoma **(Figure 1).** Clinical examination and ultrasonography revealed no evidence of axillary or inguinal lymphadenopathy. An *ex tempore* biopsy was obtained from a darker erythematous

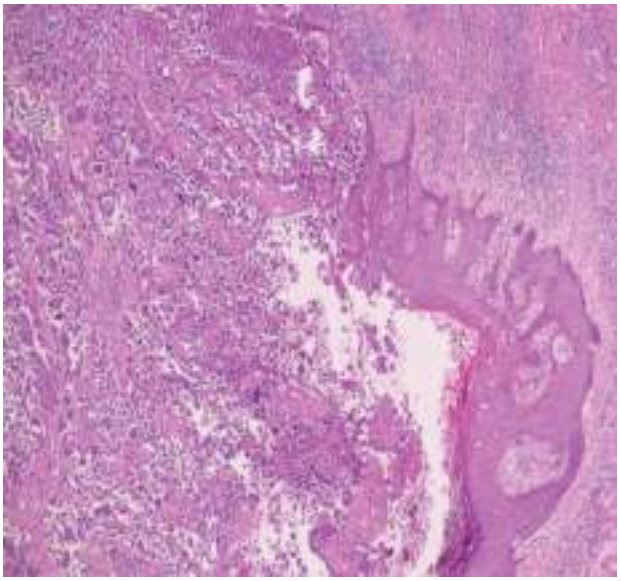

Figure 4. Border between tumor and healthy tissue

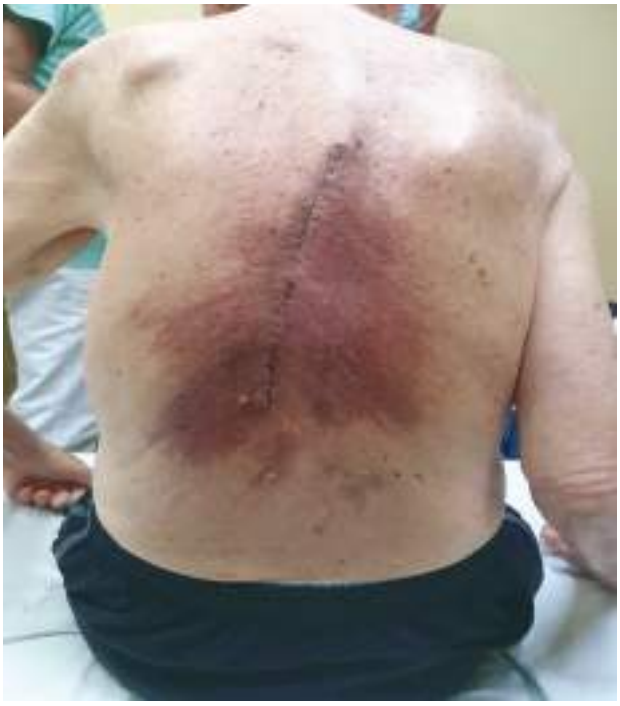

Figure 5. Fourteen days after radical excision

area at the tumor periphery to assist in margin determination; however, histopathological analysis revealed no malignant elements **(Figure 2).** The tumor was subsequently radically excised under general anesthesia with a minimum safety margin of 2.5 cm, extending to the level of the fascia. Definitive histopathological examination confirmed nodular cutaneous melanoma with a Breslow thickness greater than 10 mm and Clark level IV, accompanied by ulceration, satellitosis, and both perivascular and intravascular invasion **(Figures 3 and 4).** Based on these findings, sentinel lymph node biopsy was recommended in accordance with current melanoma guidelines; however, the patient declined further surgical intervention. The case was presented to the Oncology Committee for Soft Tissue Tumors at the Institute of Oncology of Vojvodina in Sremska Kamenica **(Figure 5).** The patient did not attend subsequent follow-up visits, and the current clinical outcome remains unknown.

Discussion

This case is notable for several clinically and diagnostically significant features. First, the tumor size and macroscopic appearance were highly unusual. The lesion presented as a large (16 cm), ulcerated, whitish, cauliflower-like mass with a narrow stalk located on the back. Such morphology is highly atypical for melanoma and represents a considerable diagnostic challenge. Giant nodular melanomas exceeding 10 cm are rare [7], and minimal or absent pigmentation further increases the likelihood of misdiagnosis or delayed diagnosis [6]. In this case, the predominantly amelanotic and exophytic appearance contributed to the initial clinical suspicion of squamous cell carcinoma.

Second, histopathological analysis revealed multiple high-risk features, including Breslow thickness >10 mm, ulceration, satellitosis, and perivascular and intravascular invasion, all of which are associated with an increased risk of regional and distant metastasis [8]. Nodular melanoma is characterized by the absence of a prolonged radial growth phase, resulting in early vertical invasion and advanced tumor thickness at diagnosis [9]. The presence of numerous mitotic figures indicates aggressive biological behavior [7].

An important limitation in this case relates to the intraoperative diagnostic approach. Frozen-section analysis (*ex tempore*) was performed based on the initial suspicion of squamous cell carcinoma and aimed to assess surgical margins. However, the biopsy was obtained from a peripheral erythematous area rather than from the most representative portion of the tumor. This likely explains the absence of malignant findings on frozen section and represents a limitation of the diagnostic approach in this case. Moreover, frozen-section analysis has inherent limitations in large, heterogeneous cutaneous tumors and is not considered reliable for the definitive evaluation of melanocytic lesions when melanoma is not clinically suspected.

Despite the extensive local tumor burden and multiple adverse histopathological features, no clinically evident regional or distant metastases were detected at presentation. Given the tumor thickness, ulceration, and satellitosis, this finding is unusual. Possible explanations include biological variability, host immune response, or differences in tumor biology; however, complete staging was not achieved, as the patient declined sentinel lymph node biopsy and further oncological evaluation.

This case underscores the importance of including melanoma in the differential diagnosis of large, ulcerated, exophytic, or amelanotic skin lesions. Adequate preoperative biopsy, thorough histopathological evaluation, and appropriate staging are essential to avoid diagnostic errors and ensure optimal management. The absence of clinically detectable metastases despite advanced local disease further enhances the educational value of this case.

Conclusion

Giant nodular melanoma may present with atypical and misleading clinical features, as illustrated by this case of a 16 cm ulcerated, predominantly whitish tumor on the back of a 78-year-old patient. The pres-

ence of high-risk histopathological characteristics – ulceration, Breslow thickness > 10 mm, satellitosis, and vascular invasion – underscores its aggressive nature. The initial misdiagnosis as squamous cell carcinoma highlights the need for heightened clinical awareness. Early biopsy, timely surgical excision with adequate margins, and appropriate staging, including sentinel lymph node evaluation, are critical for optimal management. The absence of follow-up in this case precludes assessment of clinical outcome and further emphasizes the importance of patient adherence to postoperative surveillance. Recognition of such atypical presentations may facilitate earlier diagnosis and improve prognosis.

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EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AS AN INITIAL MANIFESTATION OF LUNG CARCINOMA – A CASE SERIES

EGZACERBACIJA HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA KAO INICIJALNA MANIFESTACIJA KARCINOMA PLUĆA – SERIJA PRIKAZA SLUČAJEVA

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Abstract

Introduction. Chronic obstructive pulmonary disease is frequently accompanied by exacerbations that significantly worsen patients' clinical status. Although infections are the most common trigger, atypical, recurrent, or treatment-resistant exacerbations may indicate other underlying pathologies, including lung carcinoma. Early recognition of malignancy in patients with chronic obstructive pulmonary disease is crucial for timely initiation of therapy and improved outcomes. **Case Reports.** We present two patients with established chronic obstructive pulmonary disease in whom worsening respiratory symptoms were initially interpreted as exacerbations of the underlying disease. In the first case, chest computed tomography and bronchoscopy revealed a well-differentiated squamous cell carcinoma (stage IIIB), while in the second case histopathological analysis confirmed lung adenocarcinoma (stage IIIA). In both cases, the absence of response to standard therapy and the atypical clinical course raised suspicion of malignancy. **Conclusion.** Lung carcinoma in patients with chronic obstructive pulmonary disease patients may clinically manifest as an apparent exacerbation of the primary disease, potentially leading to diagnostic delay. Any atypical, frequent, or therapy-refractory exacerbation should prompt further diagnostic evaluation, particularly radiological assessment. Recognition of clinical "red flags," such as unexplained weight loss, hemoptysis, new-onset chest pain, or radiological changes not attributable to infection, is essential for early cancer detection and improved prognosis. Early implementation of radiological diagnostics, supported by a multidisciplinary approach, represents a key component of successful patient management.

Key words: Pulmonary Disease, Chronic Obstructive; Symptom Flare Up; Lung Neoplasms; Liquid Biopsy; Diagnosis, Differential; Early Diagnosis; Signs and Symptoms; Disease Progression; Risk Factors

Sažetak

Uvod. Hronična opstruktivna bolest pluća često je praćena egzacerbacijama koje značajno pogoršavaju kliničko stanje bolesnika. Iako su infekcije najčešći uzrok pogoršanja, atipične, učestale ili terapijski rezistentne, egzacerbacije mogu ukazivati na postojanje drugih patoloških procesa, uključujući i karcinom pluća. Pravovremeno prepoznavanje maligniteta u ovoj populaciji od suštinskog je značaja za ishod lečenja. **Prikaz slučajeva.** Prikazana su dva pacijenta sa potvrđenom dijagnozom hronične opstruktivne bolesti pluća kod kojih se pogoršanje respiratornih simptoma inicijalno tretiralo kao egzacerbacija osnovne bolesti. Kod prve pacijentkinje, nalaz kompjuterizovane tomografije i bronhoskopija otkrili su skvamozno-celularni karcinom pluća (stadijum IIIB), dok je kod drugog pacijenta dijagnostikovan adenokarcinom pluća (stadijum IIIA). U oba slučaja, odsustvo odgovora na standardnu terapiju i atipičan tok bolesti bili su ključni za sumnju na malignitet. **Zaključak.** Karcinom pluća kod bolesnika sa hroničnom opstruktivnom bolešću pluća može se klinički manifestovati kao prividno pogoršanje osnovne bolesti, što dovodi do dijagnostičkog kašnjenja. Svaka atipična, učestala ili na terapiju refraktorna egzacerbacija treba da pobudi sumnju na malignitet i zahteva dodatnu dijagnostičku obradu, naročito radiološku. Prepoznavanje „crvenih zastavica" kao što su gubitak telesne mase, hemoptizije, novonastali bol u grudima ili radiološke promene, koje se ne mogu pripisati infekciji, od suštinskog je značaja za rano otkrivanje tumora i poboljšanje prognoze. Pravovremeno sprovođenje radiološke dijagnostike, uz multidisciplinarni pristup, predstavlja ključni element uspešnog lečenja ovih bolesnika.

Ključne reči: hronična opstruktivna bolest pluća; egzacerbacija bolesti; neoplazme pluća; tečna biopsija; diferencijalna dijagnoza; rana dijagnoza; znaci i simptomi; progresija bolesti; faktori rizika

Introduction

Chronic obstructive pulmonary disease (COPD) represents one of the leading global health problems, associated with substantial morbidity. It is characterized by progressive and largely irreversible airflow limitation, accompanied by recurrent exacerbations that significantly impair patients' quality of life [1,2]. Exacerbations of COPD are most commonly triggered by respiratory infections, exposure to air pollution, or inadequate pharmacotherapy. However, atypical, frequent, or treatment-resistant exacerbations may indicate the presence of additional pathological processes, including respiratory malignancies

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Abbreviations

COPD	– chronic obstructive pulmonary disease
CT	– computed tomography
FEV_1	– forced expiratory volume in 1 second
FVC	– forced vital capacity
GOLD	– Global Initiative for Chronic Obstructive Lung Disease
IASLC	– International Association for the Study of Lung Cancer
LDCT	– low-dose computed tomography
NLST	– National Lung Screening Trial

[3]. Lung carcinoma remains one of the most common and lethal malignancies worldwide. Despite significant advances in prevention, diagnosis, and treatment, it continues to account for the highest number of cancer-related deaths globally [4]. In patients with COPD, lung cancer may clinically manifest through worsening of underlying respiratory symptoms, often leading to diagnostic delay due to overlapping clinical presentations [5]. Early tumor detection in this high-risk population is essential, as it enables timely initiation of appropriate treatment and may significantly improve clinical outcomes [6]. A strong pathophysiological association exists between COPD and lung carcinoma, primarily based on shared mechanisms of chronic inflammation, oxidative stress, and genetic susceptibility [7–9]. Chronic airway inflammation in COPD patients results in epithelial injury, fibroblast proliferation, and dysplastic changes, thereby creating a microenvironment favorable for carcinogenesis [7]. Furthermore, oxidative stress supports the concept that COPD is not merely a smoking-related risk factor but also an independent pathophysiological condition that may promote malignant transformation [8,9]. The aim of this study was to present two clinical cases in which COPD exacerbation represented the initial manifestation of newly diagnosed lung carcinoma, with particular emphasis on the importance of differential diagnosis and clinical suspicion of malignancy in patients with an atypical disease course.

Case 1

A 60-year-old woman, a long-term smoker with a 40 pack-year history, who had been treated for COPD for the previous nine years, presented to our institution with progressive dyspnea lasting fifteen days. The symptoms were accompanied by a dry, non-productive cough, without fever or signs of infection. She had previously received bronchodilator therapy and oral antibiotic for five days in an outpatient setting without clinical improvement and was therefore referred for pulmonology evaluation. At admission, the patient was receiving triple inhalation therapy consisting of an inhaled corticosteroid, long-acting beta-agonist, and long-acting anticholinergic. Her medical history included hypothyroidism and depression. She had experienced three previous COPD exacerbations, two managed on an outpatient basis and one requiring hospitalization 14 months earlier. Laboratory testing revealed elevated D-dimer levels (980 μg/L), while inflammatory markers remained within normal limits. Spirometry demonstrated severe obstructive ventilatory impairment with FEV_1 32%, FVC 67%, and Tiffeneau index 52%, corresponding to GOLD stage III. Physical examination revealed dyspnea at rest with the use of accessory respiratory muscles, while auscultation showed diffusely diminished breath sounds and prolonged expiration. Arterial blood gas analysis indicated partial respiratory insufficiency. Chest radiography demonstrated a new inhomogeneous opacity in the projection of the right middle lung field, which had not been present on imaging performed eight months earlier. Subsequent chest computed tomography revealed a soft-tissue mass surrounding the bronchus of the middle lobe, measuring 29 × 68 mm, with a central hypodense area and enlarged lymph nodes in the right hilum (up to 15 mm) and 4R mediastinal group (up to 35 mm). Bronchoscopy demonstrated an endobronchial lesion partially obstructing the bronchial lumen of the middle lobe. Histopathological examination of biopsy specimens confirmed a well-differentiated squamous cell carcinoma of the lung (stage IIIB, T3N2M0).

Case 2

A 68-year-old man, an active smoker with a 30 pack-year history, previously diagnosed with COPD three years earlier, presented with progressively worsening exertional dyspnea, more frequent cough, and unintentional weight loss of approximately 3 kg over the preceding three months. His medical history included arterial hypertension, cardiomyopathy, and myocardial infarction two years earlier. Initially, he was treated in an outpatient setting for a presumed COPD exacerbation with bronchodilators, systemic corticosteroids, and antibiotics, but without significant clinical improvement. Over the following weeks, his dyspnea progressively worsened. Notably, the clinical course differed from his previous exacerbations (two since the initial COPD diagnosis), both of which had responded well to outpatient therapy. Upon admission, the patient was dyspneic at rest, and auscultation revealed diminished breath sounds over the lower right lung field. Spirometry showed FEV_1 41%, FVC 70%, and Tiffeneau index of 56%, consistent with severe obstructive ventilatory impairment (GOLD stage III). Chest radiography demonstrated a new inhomogeneous opacity in the right basal re-

gion, which had not been present on routine imaging performed seven months earlier. Chest computed tomography revealed a non-homogeneous retrocardiac infiltrative lesion in the right lower lobe, measuring 60 × 50 × 60 mm, associated with disruption of the pulmonary parenchymal architecture and segmental bronchiectasis. The pleural space appeared clear, and mediastinal lymph nodes were not enlarged. Bronchoscopy demonstrated irregular mucosal architecture above the entrance to the upper lobe bronchus, suggestive of tumorous granulation tissue. The orifice of the posterobasal segment was completely obstructed by tumor tissue. Biopsy samples obtained from the lesion and the right basal region were submitted for histopathological analysis, which confirmed lung adenocarcinoma, stage IIIA (T3N0M0).

Discussion

In addition to the diagnostic challenges illustrated by our cases, epidemiological data strongly support the role of chronic obstructive pulmonary disease (COPD) as one of the most important high-risk conditions for lung cancer. COPD is highly prevalent in many European countries, including Serbia, and frequently coexists with long-term tobacco exposure. Beyond this shared smoking-related risk, COPD itself represents an independent carcinogenic environment characterized by chronic inflammation, oxidative stress, and structural airway remodeling, all of which contribute to malignant transformation [9,10].

These observations have important implications for lung cancer screening strategies. Although a formal national low-dose computed tomography (LDCT) screening program has not yet been implemented in Serbia, clinical practice increasingly relies on evidence derived from large randomized trials such as the National Lung Screening Trial (NLST) and the NELSON study, which demonstrated a significant reduction in lung cancer–specific mortality among high-risk smokers. Subsequent analyses have shown that patients with COPD represent a subgroup that derives particularly pronounced benefit from LDCT screening, as lung cancers are detected more frequently and at earlier, potentially curable stages compared with smokers without airflow obstruction. Data from a regional lung cancer screening initiative conducted in Vojvodina, Serbia, further highlight the importance of organized screening and the high prevalence of smoking-related risk factors among participants [11–13].

Several international recommendations, including GOLD guidelines, suggest that LDCT screening should be considered in patients with COPD and a significant smoking history, given the disproportionally high incidence of lung cancer in this population. From a clinical perspective, these findings support the concept that COPD should not be regarded merely as a comorbidity but rather as a central risk determinant when selecting candidates for lung cancer screening, alongside age and cumulative tobacco exposure [1].

In routine clinical practice, particular attention should be given to COPD patients with advanced disease (GOLD stages III–IV), frequent exacerbations, accelerated decline in lung function, or poor response to standard therapy. In such individuals, the threshold for performing additional radiological diagnostics, including LDCT, should be low, especially when the clinical course deviates from the patient's usual exacerbation pattern. In both of our presented cases, the absence of the expected therapeutic response represented the key trigger for extending the diagnostic evaluation [13].

Beyond conventional imaging, emerging diagnostic approaches may further enhance early lung cancer detection in patients with COPD. Artificial intelligence–assisted image analysis and radiomics allow quantitative assessment of subtle morphological and textural features, potentially improving the differentiation between malignant lesions and inflammatory or emphysematous changes that often complicate CT interpretation in COPD. In parallel, liquid biopsy techniques, including the analysis of circulating tumor DNA and circulating tumor cells, have demonstrated promising results in detecting malignancy even before clear radiological abnormalities become evident.

Although these advanced techniques are not yet integrated into routine clinical algorithms, their future combination with LDCT screening may prove particularly valuable in high-risk COPD populations, in whom structural lung alternations and recurrent inflammation frequently obscure early tumor manifestations. Such multimodal diagnostic strategies may help reduce diagnostic delays and improve oncological outcomes in this vulnerable patient group [14,15].

The presented cases further illustrate that lung carcinoma in patients with COPD may clinically manifest as an apparent exacerbation of the underlying disease. Such exacerbations, particularly when unresponsive to standard therapy, pose a considerable diagnostic challenge, as symptoms such as cough, dyspnea, fatigue, and functional decline are often attributed to COPD itself. Recent studies have shown that comorbidities such as COPD may significantly prolong the time to lung cancer diagnosis. An analysis conducted in England demonstrated that patients with at least one coexisting disease capable of explaining respiratory symptoms experienced, on average, a diagnostic delay of more than one month compared

with individuals without such conditions [16]. This finding underscores the importance of maintaining a high level of clinical suspicion in every atypical COPD exacerbation. Research over the past decade has further confirmed the association between frequent COPD exacerbations and an increased risk of developing lung cancer. The Norwegian HUNT study demonstrated that patients with at least one acute COPD exacerbation had nearly a threefold higher risk of subsequently developing lung carcinoma [13]. These findings suggest that exacerbations may represent not only a marker of more severe disease but also an indicator of ongoing inflammatory processes and parenchymal injury contributing to carcinogenesis. Similarly, a Danish cohort study of outpatients with COPD reported that lung carcinoma was detected more frequently – and at earlier stages – in patients undergoing regular follow-up, including annual chest radiography and prompt imaging in the event of exacerbations [17]. These observations highlight the importance of systematic monitoring and preventive diagnostics in COPD populations, which may facilitate earlier cancer detection and improve treatment outcomes [13]. Published case reports have also described patients repeatedly hospitalized for presumed COPD exacerbations in whom lung carcinoma was ultimately identified as the underlying cause [18,19]. Such observations emphasize the need for further diagnostic evaluation in patients whose clinical condition fails to improve as expected, particularly in the presence of warning signs such as unexplained weight loss, hemoptysis, chest pain, or persistent radiological abnormalities unresponsive to standard therapy. The pathophysiological link between COPD and lung carcinoma has long been recognized. Current understanding emphasizes the role of chronic inflammation, oxidative stress, structural airway remodeling, epigenetic changes, and impaired immune surveillance in the development of both diseases [20,21]. Persistent inflammatory processes in COPD may result in irreversible epithelial damage and accumulation of genetic mutations that facilitate tumor development. Recent studies indicate that LDCT screening may be particularly beneficial for patients with COPD, as the incidence of lung carcinoma in this population is substantially higher than in the general population of smokers. Prospective analyses by de Torres et al. [22,23] demonstrated that among patients with documented airway obstruction enrolled in LDCT screening programs, lung tumors were detected more frequently and at earlier stages compared with individuals without COPD. This so-called *stage-shift effect* may be explained by chronic inflammation and structural parenchymal changes in COPD that increase the likelihood of detecting clinically relevant lesions. These findings support the implementation of LDCT screening programs in carefully selected COPD patients – particularly those with a long smoking history and frequent exacerbations (defined as two or more per year requiring additional therapy or one requiring hospitalization) – while adhering to principles of rational use and individualized risk-benefit assessment.

In this context, bronchoscopy remains a pivotal diagnostic modality in patients with COPD presenting with atypical or therapy-refractory exacerbations. It enables direct visualization of endobronchial pathology and timely histopathological confirmation, thereby significantly reducing diagnostic delay. According to current recommendations, bronchoscopy should not be postponed in patients with persistent or unexplained radiological abnormalities and an unusual clinical course of exacerbation, as delayed diagnosis may directly influene disease stage and overall prognosis [6].

Conclusion

Lung carcinoma in patients with chronic obstructive pulmonary disease may clinically manifest as worsening of the underlying disease, which can lead to significant diagnostic delay because patients often cannot distinguish the symptoms of a newly developing malignancy from those related to their baseline respiratory condition. Therefore, in patients with atypical, frequent, or therapy-refractory chronic obstructive pulmonary disease exacerbations, it is essential to maintain a high level of clinical suspicion for malignancy and to promptly initiate additional diagnostic procedures, particularly radiological imaging. Early implementation of radiological diagnostics, supported by a multidisciplinary approach, represents a key component of effective management in these patients. Furthermore, growing evidence suggests that low-dose computed tomography screening in carefully selected chronic obstructive pulmonary disease patients can facilitate earlier detection of lung cancer and reduce disease-specific mortality. Integration of thorough clinical assessment with modern diagnostic modalities should therefore become an integral part of chronic obstructive pulmonary disease follow-up in order to minimize the risk of missed malignancies and improve long-term outcomes.

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