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LETTER FROM THE EDITOR
PISMO UREDNIKA

Letter from the Editor – Overview of Articles in *Medical Review*

Dear Colleagues,

It is my pleasure to introduce this issue of *Medical Review* while also drawing the attention of our readers to the previous edition, which featured several important contributions of lasting clinical and scientific relevance. We kindly invite readers to revisit that issue, where a number of articles addressed key topics across internal medicine, rehabilitation, imaging, and interdisciplinary clinical practice, offering valuable perspectives that complement and enrich the content of the present volume. Together, these consecutive issues reflect the journal's commitment to continuity, depth, and meaningful scholarly exchange across medical disciplines.

Building on the themes and discussions introduced previously, the current issue continues to explore clinically relevant questions and broader perspectives that are increasingly shaping modern medical practice. In this context, the issue opens with an editorial by Petrovic, which provides a comprehensive and forward-looking overview of geriatrics as a medical discipline.

In his *editorial*, Petrovic emphasizes the central role of comprehensive geriatric assessment, multidisciplinary teamwork, and the harmonization of educational and professional standards across Europe. He also addresses future challenges related to population ageing, including the need to adapt healthcare systems, strengthen training pathways, and motivate younger physicians to pursue careers in geriatric medicine. This contribution sets the conceptual framework for the issue by highlighting the importance of holistic, patient-centered approaches in contemporary healthcare [1].

The first *original article*, by Ovcina et al., examines bone mineral density and fracture risk in patients with psoriatic arthritis. The authors demonstrate significant associations between reduced bone density and rheumatoid factor positivity, as well as an increased fracture risk in patients with nail involvement. These findings underline the importance of recognizing skeletal fragility in inflammatory rheumatic diseases and support the consideration of routine bone health assessment as part of diagnostic and monitoring algorithms in selected patients with psoriatic arthritis [2].

In the second original study, Belopavlovic and Vulin explore the impact of chronic kidney disease on clinical presentation, echocardiographic findings, angiographic characteristics, and in-hospital outcomes in diabetic patients with acute myocardial infarction. Their results show that the presence of chronic kidney disease is associated with more severe clinical profiles, less frequent use of percutaneous coronary intervention, longer hospital stays, and significantly higher in-hospital mortality. This study highlights the need for individualized and carefully balanced management strategies in this particularly high-risk patient population [3].

The contribution by Cukanovic et al. focuses on infections caused by Group B *Streptococcus* and herpes simplex virus during pregnancy and labor. By emphasizing prevention strategies, screening, and appropriate peripartum management, the authors draw attention to the critical importance of timely recognition and multidisciplinary cooperation in reducing maternal and neonatal morbidity. This article reinforces the role of coordinated obstetric and neonatal care in improving perinatal outcomes [4].

A clinically oriented paper by Mratinkovic et al. presents the authors' experience in the treatment of Monteggia fractures in the pediatric population. By addressing diagnostic challenges, therapeutic decision-making, and treatment outcomes, the article provides practical insights that may help optimize care, reduce complications, and improve functional recovery in children with these complex injuries [5].

The *review article* by Maksimovic et al. offers a comprehensive overview of current knowledge on low-grade serous ovarian cancer. With particular emphasis on advances in molecular understanding, diagnostic approaches, and emerging therapeutic strategies, this review provides an up-to-date synthesis of evidence that is highly relevant for clinicians involved in gynecologic oncology. The authors also highlight the importance of personalized treatment approaches for this distinct tumor entity [6].

Within the *Seminars in Medicine* section, Perovic et al. address pain assessment in the most vulnerable categories of children. The authors discuss methodological, developmental, and ethical challenges related to pediatric pain evaluation and emphasize the use of age-appropriate, validated assessment tools. This contribution underscores the importance of accurate pain recognition as a prerequisite for effective and compassionate pediatric care [7].

Among the *case reports*, Jankovic et al. present ovarian torsion as a rare but clinically significant condition that frequently leads to avoidable ovarian loss due to delayed diagnosis. This case serves as an important reminder of the need for heightened clinical awareness and timely intervention in order to preserve ovarian function, particularly in younger patients [8].

Finally, Zaloznik Djordjevic et al. describe survival in a patient with postcardiotomy cardiogenic shock treated with extracorporeal membrane oxygenation (ECMO). This remarkable case illustrates the life-saving potential of advanced mechanical circulatory support when applied in carefully selected patients and managed by experienced multidisciplinary teams, highlighting the evolving role of advanced technologies in critical care medicine [9].

We hope that the contributions included in this issue will support clinical decision-making, stimulate further research, and encourage interdisciplinary collaboration. I would like to sincerely thank all authors and reviewers for their valuable work and continued dedication to the journal.

With kind regards,
Radmila Matijevic
Editor-in-Chief *Medical Review*

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EDITORIAL
UVODNIK

THE ILLUSION OF DIAGNOSTIC AGREEMENT – INSTITUTIONAL BIAS AS A HIDDEN FORCE IN MODERN MEDICINE

ILUZIJA DIJAGNOSTIČKE SAGLASNOSTI – KAKO INSTITUCIONALNA PRISTRASNOST UTIČE NA SAVREMENU MEDICINU

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Editorial
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Abstract
This editorial explores how diagnostic agreement within medical institutions may reflect shared interpretive culture rather than true diagnostic accuracy. Drawing from pathology, psychiatry, internal medicine, and medical decision science, the article argues that institutional diagnostic cultures, groupthink dynamics, cognitive imprinting during training, and anchoring effects can create the illusion of consistency that does not necessarily correspond to biological reality. The editorial also examines how central review panels and artificial intelligence systems may reproduce institutional biases unless diversity of input and multi-institutional calibration are incorporated into diagnostic processes.
Key words: Diagnosis; Bias; Institutional Practice; Artificial intelligence; Risk Factors

Sažetak
U tekstu se razmatra ideja da se visoka saglasnost među lekarima u okviru iste ustanove može zasnivati pre na zajedničkim profesionalnim navikama, obrascima razmišljanja i interpretativnim okvirima nego na stvarnoj dijagnostičkoj tačnosti. Polazeći od oblasti patologije, psihijatrije, interne medicine i nauke o medicinskom odlučivanju, članak tvrdi da faktori poput institucionalne kulture, grupnog mišljenja, obrazaca usvojenih tokom specijalističke obuke i kognitivnog „usidravanja" mogu stvoriti privid doslednosti dijagnoza koji ne mora uvek odgovarati biološkoj stvarnosti. Rad dalje analizira kako centralne ekspertne komisije i sistemi veštačke inteligencije mogu nesvesno preuzeti i reprodukovati istu vrstu institucionalne pristrasnosti, ukoliko se u dijagnostičke procese ne uključe raznovrsniji izvori stručnog mišljenja i međuinstitucionalna kalibracija.
Ključne reči: dijagnoza; pristrasnost; institucionalna praksa; veštačka inteligencija; faktori rizika

Diagnostic accuracy is a core premise of modern medical practice. Every decision – whether to biopsy, treat, surveil, discharge, or escalate care – depends on the assumption that the diagnostic categories we use are both meaningful and stable. Yet the reality is far more complex. Diagnostic error has traditionally been understood as underdiagnosis – situations in which important information is absent, overlooked, or not recognized. However, advances in highly sensitive diagnostic technologies have introduced a parallel challenge: overdiagnosis, in which abnormalities are detected that would never have caused symptoms or clinical harm. Overdiagnosis is increasingly recognized in population-based screening programs and in situations where imaging or laboratory tests are performed without clear medical indication. Together, these dual forms of diagnostic error demonstrate that diagnostic categories are not fixed biological truths but dynamic constructs shaped by evolving technology and interpretive judgment. As a result, the stability of these categories is more fragile than clinicians often realize [1–3].

Agreement among observers does not always reflect diagnostic truth. Instead, it may arise from shared assumptions and institutional habits that act as invisible forces shaping diagnostic behavior. The phenomenon is not limited to a single organ system; studies across multiple diagnostic fields show that clinicians who work within the same institutional environment, share similar case volumes, and engage in ongoing informal learning tend to demonstrate higher internal concordance [4]. Such agreement, however, often reflects a common interpretive culture rather than objective correctness. Furthermore, clinicians themselves frequently sense when their interpretations fall near diagnostic boundaries: discordance is far more likely when observers report low confidence, uncertainty, or a feeling that the case does

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not neatly fit established patterns. In real-world practice, these moments of uncertainty often prompt a second opinion or additional consultation – mechanisms known to improve diagnostic accuracy – but such safeguards are absent in controlled study environments. A recent study of "indefinite for dysplasia" in gastrointestinal mucosal biopsies illustrates this phenomenon vividly: strong internal agreement masked the possibility that shared diagnostic thresholds, rather than biological reality, were shaping the classification [5].

In that study, the authors sought to understand the natural history of indefinite lesions in the esophagus and stomach - cases in which atypia is present but insufficient for a definitive diagnosis of dysplasia. The reported progression rates were surprisingly high, particularly in the esophageal cohort. Instead of behaving like reactive or inflammatory mucosa, which theoretically should form the bulk of the indefinite category, many lesions progressed to definite dysplasia, including a meaningful number that advanced to high-grade dysplasia or carcinoma. This unexpected behavior raised an important question: were these lesions truly "indefinite," or were some of them, at baseline, subtle examples of low-grade dysplasia that were not recognized during initial interpretation [6].

To answer this, the investigators performed a central review of the original biopsies, using two expert pathologists from the same institution. Critically, nearly all cases remained classified as indefinite upon review, only a small percentage were downgraded, and none were upgraded. At first glance, this very high level of agreement appears reassuring. It suggests strong interobserver reliability, a consistent approach to diagnosis, and diagnostic confidence. However, when placed in the context of the broader gastrointestinal pathology literature, this result is atypical. Many multi-institutional studies of Barrett-related dysplasia have demonstrated extremely high variability in the evaluation of borderline lesions. When cases diagnosed as low-grade dysplasia in community practice are reviewed by panels of expert gastrointestinal pathologists from different institutions, the majority – sometimes more than sixty percent – are downgraded to either reactive or indefinite, and a smaller but important fraction are upgraded. This long-recognized variability has shaped modern surveillance algorithms and is the reason expert external review is now recommended before ablative therapy is offered. Further complicating interpretation, reviewers in prior studies have noted that when they perceived a case as difficult or diagnostically ambiguous, their inclination was to classify it as indefinite for dysplasia – even when cytologic atypia was substantial – rather than risk "overdiagnosis". As a result, a surprisingly high percentage of cases without a clear consensus diagnosis, and with relatively low average dysplasia scores, ultimately progressed to cancer at rates higher than expected [7]. These observations highlight the vulnerability of histologic interpretation when it operates without clinical context and underscore the inherent limitations of "interpretation divorced from clinical data". Yet, despite these challenges, a consistent finding across the literature remains: as the degree of dysplasia increases, so does the likelihood of detecting invasive carcinoma, with higher-grade categories associated with progression in greater numbers of patients and over shorter intervals.

In that context, a reclassification rate of only four percent in a single-institution review is not simply a sign of precision – it is almost certainly a reflection of shared diagnostic culture. Pathologists working within the same institution, attending the same consensus meetings, and reviewing difficult cases together inevitably internalize each other's interpretive boundaries. They share a similar understanding of what constitutes dysplasia, what features deserve the designation of "indefinite", and how to evaluate atypia in the setting of inflammation or regenerative change. This alignment is not intentional; it develops organically over years of shared practice, mutual teaching, and institutional tradition. It becomes an unspoken diagnostic dialect – a locally consistent set of expectations about what specific histologic patterns signify. When pathologists who share this dialect review cases, even when blinded to clinical outcomes, their diagnoses will naturally converge. Agreement within this setting is therefore an echo of shared assumptions, not evidence that those assumptions reflect biological truth. This may be supported by various studies in which diagnostic accuracy or agreement improved after a consensus training in which specific diagnostic criteria were taught and agreed upon [5,7].

The implications of institutional diagnostic harmonization are profound. First, it creates an illusion of reproducibility. High agreement within a single center, even among recognized experts, may reflect internal coherence reinforced by group-level cognitive and organizational forces rather than true diagnostic objectivity. Numerous studies in health care have shown that groupthink, driven by cohesiveness, shared training backgrounds, and hierarchical team structures, is common and promotes alignment within clinical groups. This fosters distinct diagnostic "dialects" that may diverge substantially from those of other institutions, meaning that internal concordance does not ensure external validity.

When diagnostic categories are shaped primarily by local norms rather than universally applied criteria, institutions may develop distinct thresholds for borderline lesions, resulting in clinically meaningful variation. In pathology, for example, a biopsy considered indefinite for dysplasia in one center may be interpreted as definite low-grade dysplasia in another, reflecting how departments collectively learn and internalize diagnostic thresholds. Psychiatry shows a similar pattern: diagnostic boundaries along continua – such as mood or personality disorders – are influenced by local training traditions, supervisory styles, and the diagnostic "language" of a residency program. Clinicians frequently engage in confirmatory information search, reinforcing initial impressions, and such tendencies are amplified within cohesive teams where shared mental models, longstanding habits, and groupthink dynamics encourage conformity [9].

Internal medicine provides additional evidence that hierarchy and culture shape diagnostic reasoning. Qualitative studies reveal that residents often attribute diagnostic decisions to consultants or senior team members, perceiving limited opportunities to contribute their own assessments. This hierarchical structure reduces cognitive diversity and fosters groupthink, causing junior clinicians to adopt prevailing interpretations even when alternative hypotheses come to mind. Practitioners may also diverge from guidelines when new evidence conflicts with impressions formed during training - a phenomenon rooted in cognitive imprinting and the hidden curriculum, through which the diagnostic habits and priorities of senior clinicians become enduring defaults.

Across specialties, the consequence is consistent: divergence in diagnostic philosophy directly affects treatment decisions, follow-up strategies, and patient outcomes – whether the lens is a microscope, a mental status examination, or a multidisciplinary ward round [10,11].

A second consequence of institutional diagnostic culture is the effect of anchoring bias on the observed natural history of disease. When a department adopts a particular interpretive threshold – for example, a conservative standard for diagnosing dysplasia – that threshold becomes a cognitive anchor against which all subsequent cases are judged. Borderline lesions that might be classified as dysplastic elsewhere become anchored to the local "indefinite" category. As a result, the indefinite group at that institution will inevitably show higher progression rates, not because the biology differs, but because true dysplasia was underclassified at baseline. Conversely, institutions anchored to a lower threshold for diagnosing dysplasia will observe lower progression rates in their indefinite category because fewer biologically dysplastic lesions remain within it. These anchoring effects can produce systematic, institution-specific distortions in progression data, leading to misleading impressions of disease behavior that may be incorrectly generalized to broader populations [12–14].

Third, institutional bias undermines research quality in ways that mirror well-documented group-level distortions in expertise recognition. As shown in Bunderson's 2003 study on status dynamics in work groups, groups tend to rely on familiar internal cues and shared interpretive habits rather than objective indicators of expertise, particularly when power is centralized or members share a long-standing institutional culture. Applied to pathology research, when both the original diagnosis and the "expert" review come from the same institution, reviewers are not evaluating correctness – they are replicating the institution's own status hierarchy and interpretive norms. This produces an illusion of agreement driven by shared culture rather than true diagnostic accuracy. Such designs inflate measures of concordance, obscure misclassification risk, and generate evidence that reflects the institution's diagnostic ideology rather than biologic reality. When these internally reinforced findings are then used to shape clinical guidelines or risk models, institutional bias propagates outward, amplifying local patterns of over- or under-diagnosis into system-wide practice [15].

This issue is not limited to gastrointestinal pathology. Radiology provides a particularly revealing parallel. In a recent study of nearly 1.9 million radiology reports, only 114 intra-institutional discrepant-opinion alerts were recorded – an astonishingly low rate of 0.006%, or roughly one disagreement per 16,563 reports. Yet despite this apparent harmony, more than half of these rare alerts represented major interpretive discrepancies, and over fifty percent resulted in changes to patient management. This extremely low internal discrepancy rate stands in striking contrast to the much higher discordance documented when radiologists reinterpret studies from other institutions, where disagreement rates commonly range from 7% to over 30% and where second opinions are more accurate in the vast majority of cases. This pattern suggests that intra-departmental agreement reflects a shared diagnostic culture more than true diagnostic precision [16].

In psychiatry, diagnostic tendencies align closely with training environments and training setting with consequent high agreement within departments revealing that what looks like reliability may instead be the product of local diagnostic philosophy [17].

Institutional diagnostic culture is therefore a pervasive, cross-disciplinary phenomenon. Yet it remains largely unacknowledged, perhaps because it challenges medicine's belief in its own objectivity. We are accustomed to thinking that diagnoses reflect intrinsic biological categories. But for many conditions, especially those on diagnostic continua – reactive versus dysplastic mucosa, benign versus atypical nevi, mild versus moderate psychiatric symptoms, borderline valvular stenosis – the distinction depends as much on interpretive thresholds as on biology. Those thresholds do not arise in isolation. They are shaped by training, experience, local tradition, and shared norms [18].

Recognizing institutional bias is the first step toward mitigating its effects, and solutions are well within reach. One essential approach is to increase the use of multi-institutional review panels in studies evaluating borderline or subjective diagnostic categories. When pathologists or radiologists from different institutions independently evaluate the same cases, the resulting consensus is more likely to reflect underlying biological patterns rather than the idiosyncrasies of any single department. Standardized diagnostic criteria, structured scoring systems, and ancillary testing – such as immunohistochemical markers in pathology or quantitative assessment tools in radiology – can further reduce interpretive drift. Digital pathology and cloud-based image sharing now make such cross-institutional consultation feasible at a scale that was previously unimaginable.

However, it is equally important to acknowledge that central review panels are not immune to the very biases they aim to counteract. Once a panel meets regularly, discusses cases, and negotiates shared thresholds, it begins to function like an institutional group with its own internal diagnostic culture. Empirical evidence illustrates this limitation. In a central pathology review by Spoor and Cross involving seven pathologists and 630 biopsy specimens, concordance with the original diagnoses for atypical hyperplasia was only 68%. Even more revealing, when the central review diagnoses were compared with final hysterectomy outcomes, 4.7% of cases were still misclassified despite multilayered expert review. These findings underscore that while multi-institutional review improves reliability, it does not eliminate group-level interpretive bias. Instead, it shifts the locus of bias from individual departments to newly formed expert collectives – groups that may themselves develop shared assumptions and diagnostic dialects over time [19,20].

Artificial intelligence introduces both new risks and new possibilities [21]. Machine-learning models trained on data from a single institution – or from narrow, homogeneous datasets – inevitably absorb and reproduce the diagnostic habits, thresholds, and blind spots embedded in that environment. Studies in medical AI have already shown that such models can perpetuate institution-specific biases and perform poorly when applied elsewhere, echoing the well-documented problems of algorithmic bias in criminal justice, hiring, and loan approval systems. In those domains, biased algorithms have created self-reinforcing interpretive worlds in which human insight is diminished and skepticism becomes difficult; questioning the algorithm is often perceived as questioning objectivity itself. Medicine is not immune to this risk. If uncritically deployed, AI could magnify institutional diagnostic philosophies and obscure the very uncertainty clinicians need to recognize. Yet when designed with diverse, multi-institutional training data and used deliberately, AI can serve the opposite role – quantifying interobserver variability, flagging discordant cases, and exposing where local diagnostic cultures diverge. In this way, AI can help map and ultimately correct the institutional biases that threaten diagnostic accuracy, rather than silently hardwiring them into future practice [21,22].

Ultimately, the medical community must confront a simple but uncomfortable truth: agreement within an institution is not synonymous with accuracy. It is entirely possible for a group of experts to agree consistently on a diagnosis that reflects their shared interpretive culture rather than biological fact. Only through external challenge, cross-institutional collaboration, and deliberate exposure to diverse diagnostic viewpoints can we ensure that our categories reflect disease rather than tradition. The illusion of diagnostic agreement is one of the most subtle – and most consequential – sources of variability in modern medicine. Acknowledging it is the first step toward building diagnostic systems that are truly reliable, reproducible, and aligned with the realities of patient biology.

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RE-PROGRAMMING THE INFLAMMATORY MICROENVIRONMENT OF THE SYNOVIAL JOINT IN OSTEOARTHRITIS WITH CELL THERAPY – A CONCISE UPDATE ON TISSUE-GENE-C

REPROGRAMIRANJE INFLAMATORNOG MIKROOKRUŽENJA U SINOVIJALNIM ZGLOBOVIMA SA OSTEOARTRITISOM POMOĆU ĆELIJSKE TERAPIJE – SAŽET PREGLED TISSUEGENE-C

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Editorial
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Osteoarthritis (OA) remains the most prevalent chronic joint disease globally [1], characterized by progressive articular cartilage degeneration, synovial inflammation, and debilitating pain [2,3]. Despite its profound socioeconomic impact, therapeutic strategies have historically remained limited to symptom management, such as non-steroidal anti-inflammatory drugs (NSAIDs) and, eventually, total joint replacement [4,5]. The current medical landscape urgently demands disease-modifying therapies that can halt progression, repair tissue, and address the multifaceted pathology of OA, which is now understood to be a complex mechano-inflammatory disease [6,7].

The convergence of cell biology and gene engineering is heralding a critical new era of therapeutic development for OA, exemplified by advanced therapies designed to fundamentally re-program the intra-articular microenvironment [8,12]. The next generation of OA treatment is centered on utilizing sophisticated biological agents to intervene at the molecular and cellular level. Among the most promising of these is TissueGene-C (TG-C), an allogeneic cell and gene therapy product **(Figure 1)** [13].

TG-C comprises a mixture of human allogeneic chondrocytes and a population of irradiated, genetically modified cells engineered to overexpress trans-

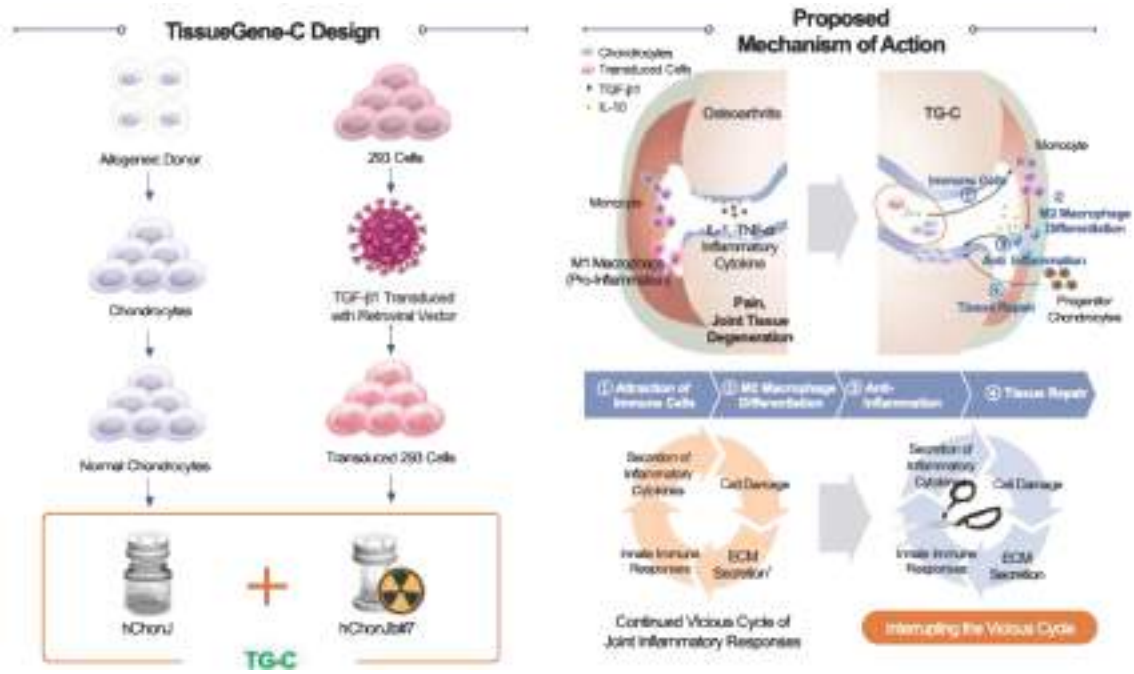

Figure 1. Design and mode of action of TissueGene-C

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forming growth factor beta 1 (TGF-b1) [14]. This dual-component approach is designed to deliver a potent therapeutic protein directly to the diseased joint, effectively turning the administered cells into localized "cellular factories" for TGF-b1 signalling. The action mechanism of TG-C is highly multimodal, targeting both the inflammatory and painful aspects of the disease. Major focus is the modulation of the synovial inflammation [15–17]. In OA, the innate immune system plays a key role and the joint capsule is often infiltrated by pro-inflammatory M1 macrophages [18–21]. Studies demonstrate that TG-C actively induces an anti-inflammatory microenvironment through the polarization of M1 macrophages towards the M2 phenotype [22]. The M2 macrophage is crucial for tissue repair and inflammation resolution, releasing anti-inflammatory cytokines and growth factors [23,24]. This shift is critically mediated by the activation of the prostaglandin E2 (PGE2) signalling pathway [25]. By boosting PGE2 activity, TG-C utilizes a powerful endogenous mechanism to resolve inflammation and promote an environment conducive to cartilage structural improvement [26]. Beyond its role in immunomodulation and structural repair, TG-C exhibits promising potential in long-term pain management [22]. OA-related pain is not merely a consequence of mechanical wear but is driven by biochemical mediators and the sensitization of peripheral sensory neurons. The research that we have done thus far indicates that TG-C induces long-term analgesic effects by directly regulating pain mediators within the joint [22]. By counteracting the effects of molecules that induce neuronal sensitization (e.g., in the dorsal root ganglion), this therapy effectively dampens the hyper-responsive state of the nerve fibres. This neurobiological effect is key to addressing the neuropathic-like component of OA pain, providing relief that is often durable and goes beyond simple chondroprotection.

The development of such advanced regenerative therapies is linked to advancements in protein production technologies. The feasibility of producing therapeutic proteins like TGF- b1 at clinical scale relies on sophisticated platforms utilizing mammalian cell lines [14,27]. These "protein production platforms," including the use of irradiated and transfected cells, are essential for ensuring the reliable and high-yield over-production of therapeutic growth factors necessary for clinical application.

In summary, cell and gene therapies, particularly those utilizing engineered cells to express potent growth factors like TG-C, represent a unique and transformative approach to OA therapy. By simultaneously resolving inflammation through M2 macrophage polarization, promoting structural repair, and reversing neuronal sensitization, these therapies offer the prospect of disease modification. For the osteoarthritis research community, the imperative is clear: we need to integrate these technical advances into translational and clinical studies and currently a Phase II clinical study of TG-C is underway, with results expected in 2026. The ongoing clinical trial of TG-C involved rigorous assessment of pain and function, and joint preservation. If successful, TG-C will become the first approved cell therapy for OA.

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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH CHRONIC WOUNDS – A COMPREHENSIVE ANALYSIS USING THE WOUND-QOL-17 INSTRUMENT

KVALITET ŽIVOTA POVEZAN SA ZDRAVLJEM KOD PACIJENATA SA HRONIČNIM RANAMA – SVEOBUHVATNA ANALIZA PRIMENOM WOUND-QOL-17 UPITNIKA

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Abstract

Introduction. Chronic wounds affect 1-2% of the population in developed countries, yet determinants of impaired health-related quality of life remain poorly characterized. This study aimed to identify independent predictors of reduced health-related quality of life in patients with chronic wounds using multivariate statistical methods. **Material and Methods.** This cross-sectional study was conducted from February to March 2025 in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* recommendations, included 106 patients with wounds persisting for more than four weeks. Health-related quality of life was evaluated using the Serbian version of the *Wound Quality of Life* instrument. Independent predictors of impaired quality of life were assessed using multivariate logistic regression with propensity score matching. **Results.** The median total Wound Quality of Life score was 2.24 (interquartile range 1.89–2.71). Venous leg ulcerations were the most prevalent wound type (42.5%), followed by diabetic foot ulcers (28.3%) and pressure ulcers (20.8%). Multivariate logistic regression identified three independent predictors of poor health-related quality of life: presence of comorbidities (odds ratio 2.78, confidence interval 1.34–5.76, p = 0.006), active smoking (odds ratio 3.12, confidence interval 1.51–6.45, p = 0.002), and wound duration > 6 months (odds ratio 2.45, confidence interval 1.18–5.09, p = 0.016). The physical domain was the most severely affected across all wound types (p < 0.001). **Conclusion.** Comorbidities, active smoking, and prolonged wound duration are independent predictors of reduced health-related quality of life in patients with chronic wounds. These findings highlight the importance of addressing modifiable risk factors and implementing patient-centered interventions.

Key words: Quality of Life; Wounds and Injuries; Chronic Disease; Surveys and Questionnaires; Multivariate Analysis; Cost of Illness; Risk Factors

Sažetak

Uvod. Hronične rane pogađaju 1–2% populacije u razvijenim zemljama, ali su analize faktora koji utiču na kvalitet života povezan sa zdravljem i dalje ograničene. Cilj ove studije bio je da identifikuje nezavisne prediktore narušenog kvaliteta života kod osoba sa hroničnim ranama primenom multivarijantnih statističkih metoda. **Materijal i metode.** U ovoj studiji preseka, sprovedenoj od februara do marta 2025. godine u skladu sa preporukama *Strengthening the Reporting of Observational Studies in Epidemiology*, učestvovalo je 106 pacijenata sa ranama koje traju duže od četiri nedelje. Korišćen je validirani srpski instrument *Wound Quality of Life*, a multivarijantna logistička regresija uz metodu podudaranja na osnovu sklonosti primenjena je kako bi se utvrdili nezavisni prediktori smanjenog kvaliteta života. **Rezultati.** Medijana ukupnog *Wound Quality of Life* iznosila je 2,24 (interkvartilni raspon 1,89–2,71). Najčešće su bile venske ulceracije (42,5%), zatim dijabetesno stopalo (28,3%) i dekubitalne rane (20,8%). Multivarijantna logistička regresija identifikovala je tri nezavisna prediktora lošeg kvaliteta života: prisustvo komorbiditeta (odnos verovatnoće 2,78; interval pouzdanosti 1,34–5,76; p = 0,006), aktivno pušenje (odnos verovatnoće 3,12; interval pouzdanosti 1,51–6,45; p = 0,002) i trajanje rane duže od šest meseci (odnos verovatnoće 2,45; interval pouzdanosti 1,18–5,09; p = 0,016). Najveće narušavanje zabeleženo je u fizičkoj dimenziji kvaliteta života (p < 0,001). **Zaključak.** Kormobiditeti, aktivno pušenje i produženo trajanje rane predviđaju smanjen kvalitet života kod osoba sa hroničnim ranama, što ukazuje na značaj intervencija usmerenih na modifikovane faktore i negu usmerenu na pacijenta.

Ključne reči: kvalitet života; povrede i rane; upitnici i ankete; multivarijantna analiza; troškovi bolesti; faktori rizika

Introduction

Chronic wounds represent a major global health burden, affecting approximately 1-2% of the population in developed countries [1,2]. Despite their substantial impact on healthcare systems and patient well-being, comprehensive analyses of the determinants of health-related quality of life (HRQoL) in this

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Abbreviations

CI	– confidence interval
DSM-5	– Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EWMA	– European Wound Management Association
HRQoL	– Health-Related Quality of Life
IPAQ-SF	– International Physical Activity Questionnaire – Short Form
IQR	– interquartile range
IWII	– International Wound Infection Institute
MMSE	– Mini-Mental State Examination
OR	– odds ratio
PUSH	– Pressure Ulcer Scale for Healing
SD	– standard deviation
STROBE	– Strengthening the Reporting of Observational Studies in Epidemiology
VIF	– variance inflation factor

population remain limited. Recent systematic reviews have highlighted critical knowledge gaps, including the lack of multivariate analyses controlling for confounding factors, limited comparative studies across wound etiologies, and absence of propensity score analyses for group balancing [3,4].

The pathophysiology of chronic wounds involves complex interactions between local and systemic mechanisms, including persistent inflammation, cellular senescence, and impaired angiogenesis [5]. These biological processes profoundly affect patients' physical, psychological, and social functioning; however, the relative contribution of clinical and behavioral factors to overall HRQoL remains insufficiently characterized. To addresses these gaps, the present study applies the Wilson-Cleary conceptual model of patient outcomes [6] to integrate biological variables, symptom burden, functional status, and patient perceptions.

The primary objective of this study was to identify independent predictors of impaired HRQoL in patients with chronic wounds using validated assessment instruments and robust statistical methodology, including propensity score matching. Secondary objectives were to explore domain-specific associations between clinical and behavioral factors and distinct dimensions of quality of life.

Material and Methods

Study Design and Ethical Approval

A prospective, observational, cross-sectional study was conducted between February and March 2025 in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [7]. The study protocol was approved by the Ethics Committee of the University Clinical Center of Vojvodina, Novi Sad, Serbia (approval number: 00-01/69-2025). Written informed consent was obtained from all participants before enrollment.

Study Population

Patients were recruited from the wound care clinic of the Emergency Center at the University Clinical Center of Vojvodina, Novi Sad, Serbia. Inclusion criteria were: age ≥18 years, presence of chronic wound lasting longer than four weeks [8], Mini-Mental State Examination (MMSE) score ≥24, and the ability to provide informed consent. Exclusion criteria were: acute or surgical wounds of less than four weeks' duration, significant occlusive arterial disease of the lower extremities, active malignancy requiring chemotherapy or radiotherapy, severe psychiatric disorders defined according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and the estimated life expectancy of less than six months.

Based on pilot data demonstrating a standard deviation of 0.65 in Wound-QoL scores, a minimum sample size of 96 participants was calculated to detect a clinically significant difference of 0.3 points between groups [9], with $\alpha=0.05$ and 80% statistical power. To account for 20% attrition, for a target sample size of 120 participants was defined.

Instruments and Measurements

The Wound-QoL-17 is a validated disease-specific instrument (Cronbach's $\alpha=0.92$) that comprises three domains: physical complaints (5 items), psychological well-being (5 items), and daily activities (6 items) [9]. The Serbian version of the instrument, previously translated, culturally adapted, and validated for Serbian-speaking populations, was used in this study. Clinical wound assessment included classification of wound etiology according to European Wound Management Association (EWMA) guidelines [10], wound severity using the Pressure Ulcer Scale for Healing (PUSH) Tool 3.0 [11], and wound surface area measurement by digital planimetry using ImageJ software [12]. Bacterial burden was evaluated based on the International Wound Infection Institute (IWII) criteria [13]. Smoking status was assessed by the Fagerström Test for Nicotine Dependence [14], while physical activity was measured using the International Physical Activity Questionnaire – Short Form (IPAQ-SF) [15].

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for skewed distributions. Categorical variables were presented as frequencies and percentages. Group comparisons were performed using the Mann-Whitney U test was used for binary variables and the Kruskal-Wallis test with post hoc Dunn's test for multiple-

Table 1. Demographic and clinical characteristics by wound type (n=106)

Characteristic	Venous ulcers (n=45)	Diabetic ulcers (n=30)	Pressure ulcers (n=22)	Other (n=9)	p-value
Age, years (mean±SD*)	59.8±12.4	66.2+11.8	64.III5.9	58.3±14.2	0.142
Male sex, n (%)	28 (62.2)	21 (70.0)	15 (68.2)	6 (66.7)	0.893
Wound (median, IQR†)	6.8 (3.9-12.3)	9.2 (5.1-16.8)	8.5 (4.8-15.2)	5.2 (3.2-10.8)	0.038
Wound surface area, cm^2 (median, IQR†)	8.5 (4.2-15.3)	12.3 (6.8-22.1)	15.8 (8.9-28.4)	7.2 (3.8-12.6)	0.012
PUSH‡ score/PUSH‡ (mean+SD*)	9.2 ±3.1	11.4+2.8	12.6+3.4	8.8±2.9	0.003
Presence of comorbidities, n (%)	22 (48.9)	30 (100.0)	18 (81.8)	5 (55.6)	<0.001
Current smokers, n (%)	15 (33.3)	12 (40.0)	8 (36.4)	3 (33.3)	0.932

*SD – Standard Deviation; †IQR – Interquartile Range; ‡PUSH – Pressure Ulcer Scale for Healing

Table 2. Wound-QoL-17 scores by domains and wound type

Domain	Total (n=106)	Venous ulcers (n=45)	Diabetic ulcers (n=30)	Pressure ulcers (n=22)	p-value
Overall score (median, IQR*)	2.24 (1.89-2.71)	2.20 (1.85-2.65)	2.28 (1.92-2.78)	2.64 (2.18-3.12)	0.018
Physical domain (median, IQR*)	2.60 (2.20-3.00)	2.50 (2.10-2.90)	2.65 (2.30-3.10)	2.85 (2.50-3.20)	0.021
Psychological domain (median, IQR*)	1.80 (1.40-2.40)	1.75 (1.35-2.30)	1.85 (1.45-2.50)	2.10(1.60-2.70)	0.082
Daily activities (median, IQR*)	2.33 (1.83-2.83)	2.25 (1.75-2.75)	2.38 (1.88-2.92)	2.67 (2.17-3.17)	0.036

*IQR – Interquartile Range

group comparisons. Associations between continuous variables were assessed using Spearman's rank correlation. Multivariate analysis was conducted using the binary logistic regression with backward stepwise elimination. Variables with $p < 0.2$ in univariate analysis were entered into the multivariate model. Multicollinearity was evaluated using the variance inflation factor (VIF < 5). Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. Propensity score matching was performed using 1:1 nearest-neighbor matching. All statistical analyses were carried out using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.0. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Participant Characteristics

Of the 134 patients screened, 120 met inclusion criteria and were enrolled. Complete datasets were available for 106 participants, yielding a response rate of 88.3%. The mean age of the study population was 62.4±13.7 years, and 66.0% were male. Venous ulcers were the most prevalent wound type (42.5%), followed by diabetic foot ulcers (28.3%) and pressure ulcers (20.8%). The median wound duration was 7.8 months (IQR 4.2-14.5), with significant differences observed among wound etiologies (p=0.038). All patients with diabetic foot ulcers had at least one comorbidity compared with 48.9% of those with venous ulcers ($p < 0.001$). Detailed demographic and clinical characteristics stratified by wound type are presented in **Table 1**.

Health-Related Quality of Life Assessment

The median overall Wound-QoL score was 2.24 (IQR 1.89-2.71), indicating a moderate impairment in health-related quality of life. Among the domains, the physical domain showed the greatest degree of impairment (median 2.60, IQR 2.20-3.00), followed by daily activities (2.33, IQR 1.83-2.83) and psychological well-being (median 1.80, IQR 1.40-2.40). Patients with pressure ulcers demonstrated the highest mean overall scores (2.64±0.63), reflecting worse HEQoL compared with those with venous ulcers (2.20±0.71, p=0.018). Complete domain-specific Wound-QoL-17 scores by wound etiology are shown in **Table 2**.

Univariate Analysis

Univariate analysis identified several variables significantly associated with Wound-QoL scores above the median, indicating poorer HRQoL. Comorbidities were present in 78.3% of patients with impaired HRQoL compared with 21.7% among those without impairment (p<0.001). Current smoking was observed in 71.4% versus 28.6% ($p < 0.001$), wound duration longer than six months in 68.5% versus 31.5% ($p = 0.003$), wound surface area greater than 10 cm^2 in 66.7% versus 33.3% ($p = 0.011$), and a PUSH score above 10 in 64.9% versus 35.1% ($p = 0.014$). A complete summary of univariate associations is provided in **Table 3.**

Multivariate Analysis and Independent Predictors

After adjustment for confounders, multivariate logistic regression identified three independent predictors of impaired HRQoL: presence of comorbidi-

Table 3. Univariate analysis of factors associated with impaired HRQoL (Wound-QoL > median)

Factor	Impaired HRQoL* n (%)	Preserved HRQoL* n (%)	p-value
Age > 65 years	28 (54.9)	23 (45.1)	0.156
Male sex	36 (51.4)	34 (48.6)	0.523
Presence of comorbidities	47 (78.3)	13(21.7)	<0.001
Current smoking	25 (71.4)	10 (28.6)	<0.001
Wound duration >6 months	37 (68.5)	17(31.5)	0.003
Wound area >10 cm^2	32 (66.7)	16 (33.3)	0.011
PUSH† score >10/PUSH† skor >10	35 (64.9)	19 (35.1)	0.014
Low physical activity	30 (60.0)	20 (40.0)	0.089

*HRQoL – Health-Related Quality of Life; †PUSH – Pressure Ulcer Scale for Healing

Table 4. Multivariate logistic regression – Independent predictors of impaired HRQoL

Predictor	Odds Ratio*	95% CI†	p-value
Presence of comorbidities	2.78	1.34-5.76	0.006
Current smoking	3.12	1.51-6.45	0.002
Wound duration >6 months	2.45	1.18-5.09	0.016

Model characteristics: Hosmer-Lemeshow test $\chi^2 = 6.42$, $p = 0.599$; Nagelkerke $R^2 = 0.342$; Classification accuracy = 75.5%
*OR – Odds Ratio; †CI – Confidence Interval

ties (odds ratio [OR] = 2.78, 95% confidence interval [CI] 1.34-5.76, p = 0.006), current smoking (OR=3.12, 95% CI 1.51-6.45, p = 0.002), and wound duration longer than six months (OR=2.45, 95% CI 1.18-5.09, p = 0.016). The model demonstrated good calibration (Hosmer-Lemeshow $\chi^2 = 6.42$, p=0.599), explained 34.2% of the variance (Nagelkerke R^2=0.342), and achieved an overall classification accuracy of 75.5%. Detailed multivariate logistic regression results are presented in **Table 4**.

Propensity Score Matching Analysis

Following propensity score matching of smokers and non-smokers (36 matched pairs), baseline characteristics were well balanced, with all standardized differences below 0.1. A statistically significant difference in Wound-QoL scores persisted, with smokers exhibiting worse scores than non-smokers (2.48 ± 0.58 vs. 2.02 ± 0.61; mean difference 0.46, 95% CI 0.22-0.70; p < 0.001), confirming the independent negative effect of smoking on HRQoL.

Domain-Specific Associations

Domain-specific analyses demonstrated distinct patterns of association. The physical domain was most strongly associated with wound surface area (β = 0.382, p < 0.001) and PUSH score (β = 0.345, p = 0.002). The psychological well-being domain was significantly associated with wound visibility (β = 0.298, p = 0.012) and social isolation score (β = 0.276, p = 0.018). Limitations in daily activities were associated with lower-extremity wound location (β = 0.321, p = 0.008) and mobility impairment (β = 0.412, p < 0.001).

Discussion

This study provides evidence for independent predictors of impaired HRQoL in patients with chronic wounds through comprehensive multivariate analysis and propensity score matching. The identification of comorbidities, active smoking, and prolonged wound duration as key determinants has important implications for both clinical practice and health policy.

Our median Wound-QoL score of 2.24 observed in our cohort is consistent with data reported in European populations, including studies from Germany (2.18) [16], but higher than those reported in Asian cohorts, such as Singapore (1.92) [17]. These differences may reflect variations in healthcare system organization and cultural perceptions of pain. The association between smoking and reduced HRQoL in our study (OR=3.12) was stronger than that reported in previous studies (OR 1.8-2.4) [18,19], which is likely attributable to the use of propensity score matching, enabling more robust controls of confounding.

Our findings are consistent with global research on HRQoL in chronic wound populations. Similar patterns have also been reported in regional studies of chronic conditions, where pain intensity, functional impairment, and the presence of comorbidities consistently emerge as major determinants of reduced quality of life. These convergent findings support the broader concept that chronic, mobility-limiting health problems – irrespective of underlying etiology – produce parallel declines across physical, emotional, and social domains of HRQoL, closely mirroring the determinants identified in the present study [20,21].

A study by Dantas et al. [22] similarly identified comorbidities and prolonged wound duration as major predictors of impaired HRQoL in a Brazilian cohort. Their findings, demonstrating the strong influence of metabolic and cardiovascular comorbidities on physical functioning, closely parallel our results. The stronger predictive estimates in our study may be explained by the application of propensity score matching, whereas their analysis relied solely on conventional multivariate regression.

Zhang et al. [23], in a study of 223 Chinese patients assessed using the Wound-QoL instrument, identified large wound size (≥ 100 cm^2), lower-limb location, and psychological distress (anxiety, depression) as the most influential determinants of HRQoL. Although our study highlighted smoking, comorbidities, and wound duration as primary predictors, both studies reinforce the multidimensional nature of HRQoL impairment. Observed differences likely reflect disparities in healthcare systems, wound-care accessibility, and cultural perceptions of pain and illness. Notably, our median Wound-QoL score more closely resembled those reported in European populations than in Asian cohorts, suggesting that systemic and cultural factors influence HRQoL outcomes.

The strong association between comorbidities and impaired HRQoL operates through multiple pathophysiological pathways. Systemic inflammation, characterized by elevated pro-inflammatory cytokines in conditions such as diabetes and cardiovascular diseases, impairs fibroblast activity and collagen synthesis [24]. In addition, microvascular dysfunction reduces tissue perfusion by approximately 30-40% [25]. The propensity score analysis confirmed the association between smoking and HRQoL impairment. Tissue hypoxia, mediated through carboxyhemoglobin formation, reduces oxygen delivery, while nicotine-induced vasoconstriction decreases perfusion within one hour of cigarette consumption. Moreover, immune dysfunction manifests through impaired neutrophil migration and macrophage function [26,27].

Based on these findings, a risk-stratified model of care is proposed. Patients at high risk (three or more risk factors) should receive intensive, multidisciplinary management, including weekly clinical reviews, advanced therapies, and smoking cessation support. Patients at moderate risk (one to two risk factors) should be managed in specialized wound clinics with biweekly follow-up and enhanced patient education. Low-risk patients without identifiable risk factors require monthly follow-up and self-management support.

Several limitations should be acknowledged. The cross-sectional design precludes causality inference, although the use of propensity score matching strengthens the robustness of the observed associations. As a single-center study, external validity may be limited. Behavioral variables were self-reported and may be subject to reporting bias. Furthermore, the absence of biomarker data and longitudinal follow-up precludes assessment of HRQoL trajectories over time. Future research should incorporate longitudinal cohort designs, cluster-randomized trials of risk-stratified interventions, and predictive models integrating biomarkers.

Conclusion

This comprehensive analysis identifies comorbidities, active smoking, and prolonged wound duration as independent predictors of impaired Health-Related Quality of Life in individuals with chronic wounds. The implementation of risk-stratified care pathways, integrated smoking-cessation programs, and optimized management of comorbid conditions is essential to improve patient-centered outcomes. These findings support the development of specialized, multidisciplinary chronic wound centers capable of addressing the complex interaction of factors that influence patient quality of life. Priority should be given to targeted interventions addressing modifiable risk factors, particularly smoking cessation and optimized control of comorbid diseases.

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OUTCOME PREDICTORS OF CARPAL TUNNEL RELEASE SURGERY

PREDIKTORI ISHODA HIRURŠKOG LEČENJA SINDROMA KARPALNOG TUNELA

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Abstract

Introduction. Open surgical decompression is considered the most efficient treatment for carpal tunnel syndrome and is associated with excellent outcomes in approximately 70-90% of cases. This study aimed to determine whether a correlation exists between potential predictors of postoperative outcomes and patient satisfaction following surgical procedure. **Material and Methods.** This retrospective study utilized data collected from the database of the University Clinical Center of Vojvodina and supplemented by telephone interview. Four categories of potential predictors were analyzed: patient-related factors, comorbidity-related factors, clinical findings, and other relevant factors. **Results.** A statistically significant positive correlation was identified between patient gender and postoperative satisfaction scores. Additionally, pain intensity, nocturnal pain, and postoperative complications demonstrated statistically significant negative correlations with satisfaction scores. **Conclusion.** Understanding predictors of surgical outcomes can assist patients in making informed decision regarding treatment and in setting realistic expectations about functional recovery following carpal tunnel decompression.
Key words: Carpal Tunnel Syndrome; Treatment Outcome; Decompression, Surgical; Patient Satisfaction; Recovery of Function

Sažetak

Uvod. Otvorena hirurška dekompresija kod sindroma karpalnog tunela predstavlja najefikasniji vid lečenja. To je najčešće izvođena terapijska metoda, sa oko 70–90% odličnih ishoda. Ova studija ima za cilj da utvrdi da li postoji korelacija između potencijalnih prediktora ishoda i zadovoljstva pacijenta rezultatom operativnog zahvata. **Materijal i metode.** U ovoj retrospektivnoj studiji podaci su prikupljeni iz informacionog sistema Univerzitetskog kliničkog centra Vojvodine i putem telefonskog intervjua. Analizirane su četiri kategorije potencijalnih prediktora: faktori u vezi sa ispitanikom, faktori u vezi sa komorbiditetima ispitanika, faktori u vezi sa kliničkim nalazom i ostali faktori. **Rezultati.** Utvrđena je statistički značajna pozitivna korelacija između pola i zadovoljstva ispitanika ishodom operacije, kao i negativna korelacija između bola, noćnog bola i nastanka postoperativnih komplikacija sa pacijentovom ocenom ishoda. **Zaključak.** Poznavanje prediktora ishoda može da olakša pacijentima donošenje informativne odluke o modalitetu lečenja i prilagođavanje očekivanja o funkcionalnom oporavku.
Ključne reči: sindrom karpalnog tunela; ishod lečenja; hirurška dekompresija; zadovoljstvo pacijenta; funkcionalni oporavak

Introduction

Carpal tunnel syndrome (CTS) is a compressive neuropathy resulting from mechanical-ischemic injury of the median nerve, caused by a disproportion between the size of the carpal canal and its contents. The canal is formed by the carpal groove – bounded laterally by the tubercle of the scaphoid and the tubercle of the trapezium, and medially by the pisiform and the hook of the hamate – while its roof consists of the flexor retinaculum and the distal portion of the antebrachial fascia [1]. CTS occurs more frequently in women (2.5:1), most commonly between the ages of 40 and 60. Numerous systemic and local factors contribute to its development, including repetitive wrist movements and occupational strain, acromegaly, renal insufficiency and dialysis, amyloidosis, myxedema, diabetes mellitus, pregnancy, menopause, rheumatoid arthritis, as well as wrist fractures, tenosynovitis, palmar infections, and burns [2]. Obesity has also been identified as a significant risk factor. Each one-unit increase in body mass index (BMI) – equivalent to a weight gain of 2.7 kg in an average individual – increases the risk of CTS by approximately 8%. Several mechanisms have been proposed to explain this association: work environments often designed for individuals of average body dimensions may inadequately accommodate people with higher BMI; obesity predisposes of arthritis; and increased adipose tissue may further reduce carpal tunnel capacity. Another major occupational factor is daily exposure to vibrating tools, which may cause both direct nerve injury through vibration and ischemic nerve damage via secondary vasoconstriction [3].

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Abbreviations

CTS	– carpal tunnel syndrome
EMNG	– electromyoneurography
ICD-10	– 10th revision of the International Classification of Diseases
BMI	– body mass index
RA	– rheumatoid arthritis

Clinically, CTS is characterized by pain and dysesthesia, typically affecting the first three and a half digits, with possible radiation into the forearm. Symptoms are most intense at night, frequently waking patients. In advanced cases, examination may reveal thenar muscle atrophy. Diagnostic challenges arise because subjective complaints often do not correspond with objective findings. Provocative tests, such as Tinel's and Phalen's, show greater sensitivity and specificity in advanced disease, but their diagnostic accuracy decreases considerably in early stages when dysesthesia is the predominant symptom. Electromyoneurography (EMNG) remains the most reliable diagnostic method. Differential diagnosis must exclude C6–C7 radiculopathy, which may mimic sensory deficits, and T1 radiculopathy, which can lead to thenar atrophy [4].

Treatment begins with conservative measures: management of underlying systemic conditions, reduction of occupational strain, nighttime splinting in a neutral position, and local corticosteroid injections. Long-term use of diuretics, nonsteroidal anti-inflammatory drugs, or oral corticosteroids is not supported by the literature [5]. Surgical treatment – open decompressive retinaculotomy – is indicated when conservative therapy fails or when sensory and motor deficits (with or without thenar atrophy) are present [5]. Decompression is achieved by transection of the flexor retinaculum. Open surgical decompression remains the gold standard because it allows complete visualization of the region, adaptation to anatomical variations, and protection of neurovascular structures. It is considered safe and reliable, with high rates of functional recovery and patient satisfaction; up to 85% of patients return to their previous occupation following the procedure and rehabilitation [6]. Approximately 10% of patients, however, experience poor outcomes including persistent or recurrent symptoms, or the appearance of new symptoms. Endoscopic resection of the retinaculum is also used, and although postoperative pain may be less pronounced with this technique, overall outcomes are comparable [7]. Some studies favor the endoscopic approach because due to return to work, an important consideration in predominantly working-age population, but the final decision depends on the surgeon recommendation and patient preference [8].

The severity of clinical symptoms plays a central role in the decision to operate. Symptoms tend to be more severe in obese patients and those with vitamin B12 deficiency. Among patients with more pronounced symptoms, diabetes mellitus is more common, although this correlation is not statistically significant. While occupation is a known risk factor for the development of CTS, it has not been shown to influence symptom severity [9]. A review of prognostic studies on surgical outcomes in median nerve compressive neuropathy classified potential predictors into four groups: patient-related factors, comorbidities, clinical or physical findings, and other factors such as duration of paid sick leave [10].

All factors associated with the onset of CTS, the severity of symptoms, and the choice of treatment ultimately influence surgical outcomes, quality of life, and patient satisfaction. Identifying predictive factors enables clinicians to establish realistic expectations for patients regarding functional recovery and supports informed decision-making. Furthermore, understanding these predictors allows for individualized treatment planning, potentially improving surgical effectiveness and patient satisfaction through improved quality of life. Awareness of these predictors may also guide refinements in operative and postoperative management.

The aim of this study was to determine whether selected potential predictors are associated with patient-reported satisfaction following surgical decompression for CTS. The analyzed predictors included age, sex, occupation, hobbies, lifestyle habits, comorbidities and precipitating conditions, severity of clinical symptoms and EMNG findings, type of treatment, postoperative management and patient compliance, postoperative complications, and preoperative expectations.

Material and Methods

This retrospective study was conducted over a four–year period, from January 2020 to January 2024, and included patients diagnosed with carpal tunnel syndrome who underwent surgical treatment at the Clinic for Plastic and Reconstructive Surgery, University Clinical Center of Vojvodina, Novi Sad. Clinical information was extracted from the hospital information system and supplemented through telephone interviews. The study was approved by the Ethics Committee of the University Clinical Center of Vojvodina (No. 00-258, November 16, 2023). Patients were identified using a diagnosis-based search in the hospital database, selecting those coded as G56.0 – Carpal Tunnel Syndrome according to the 10th revision of the International Classification of Diseases (ICD-10).

Potential predictors of outcome following open surgical decompressive retinaculotomy were selected based on previously published literature and classified into four categories: patient-related factors, comorbidity-related factors, clinical findings, and other contributing factors.

1. *Patient-related factors*

The analyzed patient-related variables included age, sex, and body mass index (BMI), calculated as body weight divided by body height squared (kg/m²).

2. *Comorbidity-related factors*

Comorbid conditions potentially influencing the outcome of surgical decompression were evaluated. These included: diabetes mellitus, thyroid disorders, rheumatoid arthritis, menopause, pregnancy, use of oral contraceptives or hormone replacement therapy, thoracic outlet syndrome, cervical spine disorders, gout, poor general health status, presence of an arteriovenous fistula for hemodialysis, and lifestyle habits such as smoking and excessive alcohol consumption.

3. *Clinical findings*

Clinical parameters assessed were: the presence and duration of symptoms, electromyoneurography (EMNG) findings, thenar eminence muscle atrophy, identification of hourglass deformity, neurolysis, and postoperative physiotherapy.

4. *Other factors*

Additional predictors included occupation, the possibility of taking medical leave, the surgical technique performed, and the occurrence of postoperative complications. Patient expectations and satisfaction with the surgical outcome were also analyzed.

Satisfaction was assessed via telephone interview, during which 101 respondents rated their outcome on a 1-5 scale, with 5 indicating the highest level of satisfaction.

Data were recorded in Microsoft Excel and analyzed using SPSS statistical software. After assessing the distribution of variables with Kolmogorov–Smirnov test, statistical analysis was performed using Spearman's rank correlation coefficient for continuous variables and biserial correlation for dichotomous variables. A p-value < 0.05 was considered statistically significant.

Results

From January 2020 to December 2023, a total of 202 decompressive median nerve retinaculotomies were performed at the Day Hospital of the Clinic for Plastic and Reconstructive Surgery, University Clinical Center of Vojvodina. Of the operated patients, 72.8% (n = 147) were women and 27.2% (n = 55) men. The mean age was 64 ± 12 years (range: 30–93). The mean satisfaction score with the final surgical outcome was 4.06.

1. Patient-related factors

A weak negative correlation was observed between age and satisfaction with surgical outcome ($\rho = -0.174$), though it did not reach statistical significance ($p > 0.05$, $p = 0.086$). The mean height of participants was 170.5 ± 8 cm, mean body weight 78.6 ± 11.5 kg, and mean BMI 26.9 ± 3 kg/m². BMI showed a weak negative, non-significant correlation with surgical outcome ($\rho = -0.141$, $p = 0.166$). A statistically significant positive correlation was found between sex and surgical outcome ($\rho = 0.241$, $p < 0.05$, $p = 0.017$). Female patients reported a higher mean satisfaction score (4.2/5), approximately 15% greater than that of male patients (3.65/5).

2. Comorbidity-related factors

Among the 101 surveyed patients, 20 had diabetes mellitus, 19 had thyroid disorders, 4 had rheumatoid arthritis, 17 had cervical spine disease, 8 had gout, 1 had thoracic outlet syndrome, and 1 was undergoing dialysis via an arteriovenous fistula.

Of the 66 female respondents, 37 were postmenopausal, 50 had experienced at least one pregnancy, 8 used oral contraceptives, and 3 were receiving hormone replacement therapy. Additionally, 42 respondents were smokers and 8 reported regular alcohol

Table 1. Comorbidity-related potential predictors

Potential predictor	Spearman correlation coefficient (ρ)	p
Diabetes	-0.001	0.995
Thyroid dysfunction	-0.066	0.519
Rheumatoid arthritis	-0.118	0.248
Cervical spine disease	0.013	0.903
Gout	-0.069	0.497
Menopause	-0.171	0.257
Pregnancy	-0.03	0.822
Oral contraceptives	0.251	0.1
Excessive alcohol consumption	-0.119	0.254
Smoking	-0.189	0.066

consumption. Overall, comorbidities showed no significant correlated with surgical outcome ($\rho \approx 0$, $p > 0.05$). Among women, menopause demonstrated a weak negative correlation with surgical outcome ($\rho = -0.171$), but this was not statistically significant ($p > 0.05$). Lifestyle factors such as smoking and alcohol use also showed weak, non-significant negative correlations with surgical outcome ($p > 0.05$) **(Table 1).**

3. Clinical findings

The average duration of symptoms prior surgery was 3.5 years. Symptom duration did not correlate significantly with postoperative outcome ($p = 0.691$). Pain ($\rho = -0.3$, $p < 0.01$, $p = 0.002$) and nocturnal pain ($\rho = -0.267$, $p < 0.01$, $p = 0.008$) were both significantly and negatively correlated with surgical outcome. Other clinical parameters demonstrated only weak, non-significant correlations.

4. Other factors

Additional variables included postoperative complications, bilateral hand involvement, and preoperative expectations. Postoperative complications occurred in 9 patients (8%) and were significantly associated with poorer outcomes ($\rho = -0.395$, $p < 0.01$). Bilateral symptoms showed no correlation with final outcome ($\rho \approx 0$). Expected outcome demonstrated a weak positive, non-significant correlation with postoperative satisfaction ($\rho = 0.148$).

Discussion

In this study, we examined a range of factors previously identified in the literature as potential predictors of patient satisfaction following open decompressive carpal tunnel release. The aim was to identify patients at greater risk of suboptimal surgical outcomes based on negative predictors, thereby enabling more detailed preoperative counseling and more accurate adjustment of expectations regarding treatment results.

Carpal tunnel syndrome (CTS) is the most common compressive neuropathy [11]. Previous population studies show a bimodal age distribution, with incidence peaks at 50–54 and 75–84 years [12]. Older patients demonstrate more pronounced thenar muscle atrophy, a higher frequency of nocturnal paresthesias and pain, and more marked sensory and motor neuron loss [13].

Blumenthal et al. reported a higher prevalence of muscle weakness, atrophy, and electrophysiological abnormalities in older adults, although subjective symptoms and hand function impairment did not differ significantly, suggesting that diagnosis in the older patients should rely more heavily on objective findings rather than patient-reported symptoms [14].

Although these data indicate age as a possible predictor of outcome, we did not establish a statistically significant correlation between age and postoperative satisfaction. Townshend et al. and Hobby et al. reported poorer outcomes in patients older than 60 years with more severe the symptoms [15,16].

CTS predominantly affects women, who often report more severe symptoms [17]. Mondelli et al. found more intense symptoms in women without corresponding clinical or electrophysiological severity [18]. Some authors attribute the higher incidence among women to a presumed tendency toward symptom exaggeration [19], while studies from India emphasize occupational factors and intensified manual labor as contributors to the higher prevalence and severity in women [20–22].

In our study, female participants reported significantly higher satisfaction with the final surgical outcome than male patients (average score 4.2/5 vs. 3.65/5), despite having a longer duration of symptoms prior to surgery (average symptom duration 3.7 years). This correlation reached statistical significance, indicating that female sex may be associated with more favorable subjective outcomes.

Conversely, Hobby et al. reported no sex-based differences in postoperative results despite more severe symptoms and functional limitations in women [16].

Body mass index (BMI) is well established as a risk factor for CTS development, likely because increased adipose tissue elevates the volume of structures within the carpal tunnel [23–25].

Obese individuals (BMI > 29) have a 2.5-fold higher risk of developing CTS compared to those with a BMI < 20 [26].

While high BMI is consistently linked to CTS onset, our findings showed only a weak, non-significant negative correlation between BMI and postoperative outcome, indicating that BMI is not a predictor of surgical success.

The literature similarly lacks strong evidence that age, BMI, or sex independently influence postoperative outcome following open carpal tunnel decompression, although results may be less predictable in patients > 70 years; nevertheless, high satisfaction in this group confirms the benefit of surgery when appropriate counseling is provided [10].

CTS occurs in up to one-third of diabetic patients (33%), ten times more often than in the general population [27–29]. Despite the higher incidence in this population, predicting surgical outcome remains challenging. Phalen [30] and Choi & Ahn [31] found no direct association between diabetes and postoperative function, with most patients achieving satisfactory improvement. Al-Qattan et al. reported that

approximately one-quarter of diabetic patients experience persistent postoperative numbness, often despite minimal or mild abnormalities on preoperative nerve conduction studies [32].

Thyroid dysfunction – particularly hypothyroidism – is also cited as a risk factor for CTS, potentially due to mucinous or mucopolysaccharide deposition around the median nerve or synovial edema in uncontrolled hypothyroidism [33]. Obese hypothyroid patients are considered especially susceptible [34].

Rheumatoid arthritis (RA) contributes to CTS pathogenesis but is not consistently associated with poorer postoperative outcome [35,36], although RA patients may show increased median nerve cross-sectional area, which tends to decrease with disease duration [37].

Studies indicate that up to 81% of patients with unsatisfactory outcomes following median nerve decompression also exhibit symptoms and/or signs of cervical radiculopathy, a condition referred to as double crush syndrome [38]. This syndrome represents the coexistence of cervical spine lesion and carpal tunnel syndrome, and although its clinical relevance is debated, the proposed mechanism involves proximal disruption of axonal transport that predisposes the distal nerve segment to dysfunction [39].

Despite their coexistence, the severity of the two conditions is generally not correlated; however, evaluation of both is recommended due to their frequent concurrence [40]. Importantly, even patients with EMG-confirmed double crush syndrome may achieve good or even excellent postoperative outcomes [31].

Gout is an extremely rare cause of carpal tunnel syndrome. Tophi may accumulate within flexor tendons, tendon sheaths, the floor of the carpal tunnel, or even the median nerve itself, producing pain, numbness, and weakness [41].

In our study, we examined the correlation between these comorbidities and patient-reported surgical outcome, and no association was found ($\rho \approx 0$). Thus, comorbidities did not appear to limit surgical success or influence the choice of treatment modality.

Some studies have shown that patients with concomitant thoracic outlet syndrome have markedly poor outcomes after carpal tunnel decompression, with up to 80% experiencing unfavorable results [35]. In our cohort, only one patient had this diagnosis, preventing a meaningful analysis.

Similarly, although an arteriovenous fistula is the preferred vascular access for hemodialysis, a recognized but underreported complication is hand numbness and paresthesia consistent with carpal tunnel syndrome, possibly due to venous hypertension and the steal phenomenon causing microischemia [42].

Only one patient in our study was undergoing dialysis, precluding analysis; however, the literature suggests that full functional recovery may still be expected [43].

Although our findings did not demonstrate correlations between patient comorbidities and surgical outcome, other studies have reported such associations. Because surgical treatment is typically reserved for more advanced cases requiring thorough preoperative evaluation, comorbidities may be detected during the diagnostic process [44]. A more robust assessment of their impact would require a larger sample size. Poor general health is also cited as a potential predictor of suboptimal outcome and higher postoperative complication rates [45,46].

A limitation of our study is its retrospective design, which did not allow standardized preoperative assessment using validated scoring systems. Additionally, although menopause, pregnancy, oral contraceptive use, and hormone replacement therapy are recognized risk factors for developing carpal tunnel syndrome [35], none of these factors were identified as predictors of poor postoperative outcome in our study.

We also assessed lifestyle-related predictors such as cigarette smoking and frequent alcohol consumption (more than two drinks per day). Nancollas [47] reported poorer functional recovery and persistent symptoms in smokers and heavy alcohol users; however, we found only weak, non-significant negative correlations.

According to some authors, early decompression of the affected nerve is essential for complete recovery [31,48], while others argue that symptom duration does not significantly affect postoperative outcome [49]. Consistent with the latter, our study showed no correlation between symptom duration and outcome. In contrast, symptom severity – especially pain and nocturnal pain – may be considered predictors of poorer perceived results.

Electromyoneurography (EMNG) abnormalities have not been consistently associated with surgical outcome [50], even though EMNG is widely regarded as the diagnostic gold standard [51]. Our results similarly showed a weak but non-significant negative correlation.

Arons et al. [52] conclude that the presence of "hourglass" deformity of the median nerve is not considered a negative prognostic factor. Atrophy of the abductor pollicis brevis is linked in some studies to poorer outcomes and persistent postoperative numbness [49,53], although Mondelli et al. reported that satisfactory clinical and electrophysiological improvement is still achievable [54].

We found no association between surgical outcome and the presence of hourglass deformity, abductor pollicis brevis atrophy, or postoperative physiotherapy, aligning with the findings of Pomerance and Fine [55], who reported no differences in return-to-work time or functional improvement with physiotherapy

Finally, many cited studies are based on low-level evidence. The lack of robust, consistent predictors highlights the need for well-designed prospective studies to better identify parameters that influence outcomes following open carpal tunnel decompression. Such evidence would enable more accurate prognostication and support informed decision-making for both patients and surgeons.

Conclusion

Among the analyzed parameters, a significant correlation was found with patient sex, with female sex emerging as a positive predictor of surgical outcome. In contrast, the presence of pain and nocturnal pain in the clinical presentation, as well as the occurrence of postoperative complications, were identified as negative predictors of patient satisfaction following surgical treatment of carpal tunnel syndrome. Recognizing these factors enables more accurate patient counseling regarding treatment expectations and helps clinicians individualize both therapy and postoperative care, ultimately improving the quality and efficiency of management. Furthermore, it facilitates the identification of patients at increased risk of complications and supports more effective clinical decision-making in their follow-up.

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BEYOND RECRUITMENT – A DEFERRAL ANALYSIS REVEALS THE KEY TO A SUSTAINABLE BLOOD SUPPLY

ANALIZA ODBIJANJA DAVALACA KRVI – KLJUČ ZA DUGOROČNO STABILNO SNABDEVANJE KRVLJU

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Abstract

Introduction. Blood donor deferral, although essential for ensuring transfusion safety, represents a significant challenge to donor retention and overall blood supply. Understanding its causes and demographic patterns is crucial for developing effective interventions. **Material and Methods.** A retrospective cross-sectional study was conducted at the Blood Transfusion Institute of Vojvodina, including all voluntary blood donors from January to December 2024. Collected data encompassed demographic characteristics, donor status, and reasons for temporary or permanent deferral. Descriptive statistical methods were applied. **Results.** Among 15,791 donor candidates, 1,957 (12.39%) were deferred. Most deferrals were temporary. Low hemoglobin was the leading cause, predominantly affecting women and younger donors. Notably, the majority of deferred individuals were repeat donors. Other common reasons included medication use and acute infections. Over 90% of all deferrals were due to temporary conditions, indicating substantial potential for donor return with appropriate follow-up and management. **Conclusion.** Donor deferral is primarily driven by reversible health factors. Targeted improvements in pre-donation screening, donor education, and iron deficiency prevention could reduce avoidable deferrals. Importantly, the manner in which deferred donors are approached significantly influences their likelihood of returning. Ensuring empathetic communication and clear guidance is essential for maintaining a stable and sustainable blood supply.
Key words: Blood Donors; Blood Safety; Donor Selection; Eligibility Determination; Risk Factors

Sažetak

Uvod. Odbijanje davalaca krvi, iako neophodno radi sigurnosti transfuzije, predstavlja izazov za očuvanje baze davalaca i stabilnost zaliha krvi. Razumevanje uzroka i demografskih obrazaca može doprineti efikasnijem planiranju i sprovođenju mera za unapređenje davalaštva. **Materijal i metode.** Retrospektivna studija preseka sprovedena je u Zavodu za transfuziju krvi Vojvodine tokom 2024. godine. Analizirani su podaci svih dobrovoljnih davalaca krvi, uključujući demografske karakteristike, status davaoca i razloge za privremeno ili trajno odbijanje. **Rezultati.** Od ukupno 15.791 prijavljenih, 1.957 je bilo odbijeno. Većina odbijanja bila je privremena. Najčešći uzrok bila je niska koncentracija hemoglobina, posebno kod žena i mlađih davalaca. Zanimljivo je da su većinu odbijenih činili redovni davaoci. Ostali uzroci uključivali su upotrebu lekova i akutne infekcije. Više od 90% odbijanja odnosi se na privremene faktore, što ukazuje na mogućnost ponovnog angažovanja tih davalaca. **Zaključak.** Većina uzroka odbijanja davalaca je privremena. Ciljane mere poput unapređenja skrininga, edukacije i prevencije deficita gvožđa mogu smanjiti broj nepotrebnih odbijanja. Ključno je kako se postupa sa odbijenim davaocima gde su empatija i jasna komunikacija od presudnog značaja za njihovo vraćanje i očuvanje stabilnih zaliha krvi.
Ključne reči: donori krvi; bezbednost krvi; izbor donora; utvrđivanje podobnosti; faktori rizika

Introduction

Blood donation represents a cornerstone of modern healthcare and is essential for a wide range of life-saving medical interventions, including surgical procedures, trauma care, management of anemia, hematologic and oncologic malignancies, and pregnancy-related complications [1]. Ensuring a safe and adequate blood supply remains a critical and continuous challenge for transfusion services worldwide. These services must carefully balance two often competing priorities: maintaining sufficient blood inventory to meet clinical needs while rigorously safeguarding the health of both recipients and voluntary donors [2]. A key mechanism for achieving this balance is meticulous donor selection through pre-donation screening. This process, guided by national and international standards, results in the temporary or permanent deferral of individuals who do not meet established eligibility criteria [3]. Donor deferral is indispensable for minimizing the risk of transfusion-transmissible infections and for protecting donor health, particularly among

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those who may be vulnerable to adverse events during or after donation [4]. However, deferral also poses a substantial operational challenge. High deferral rates reduce the availability of blood units, increase operational costs, and lead to inefficient use of resources [5]. Additionally, deferral can negatively affect donor motivation; many individuals perceive the experience as discouraging, which may decrease their willingness to donate again and thereby undermine donor pool stability [6]. Patterns and causes for deferral vary considerably across regions and populations. These differences reflect the local epidemiology of infections, genetic factors, socio-cultural practices, and differences in regulatory frameworks [7,8]. As such, regional assessment of deferral patterns is essential. Identifying the predominant causes of deferral within a specific population enables transfusion services to optimize donor education, refine recruitment strategies, and implement targeted interventions aimed at reducing avoidable deferrals while upholding safety standards [9]. This study aims to provide a comprehensive analysis of blood donor deferrals at the Blood Transfusion Institute of Vojvodina. The primary objectives are to determine the overall deferral rate, identify the most common reasons for temporary and permanent deferral, and evaluate key demographic characteristics of deferred donors, including age, gender, and donor status. By identifying the main sources of donor loss, the study seeks to generate evidence-based recommendations to minimize unnecessary deferrals, improve donor retention, and ultimately strengthen the sustainability and resilience of the regional blood supply system.

Material and Methods

Study Design and Setting

A retrospective cross-sectional study was conducted using records of all voluntary blood donor presentations at the Blood Transfusion Institute of Vojvodina from January 1 to December 31, 2024. The institute serves as a tertiary-level center responsible for blood collection and distribution across the entire Vojvodina region.

Study Population and Donor Screening

The study population included all individuals who presented as voluntary blood donors during the study period. Each donor underwent standardized pre-donation screening in accordance with the Serbian Ministry of Health's *Rulebook on Blood and Blood Component Donors*. This multi-step process included:

1. Registration: Documentation of basic demographic information.

2. Health History Questionnaire: A self-administered form covering medical history, current health status, lifestyle factors, risk behaviors (e.g., travel, tattoos, piercings), and medication use.

3. Preliminary Health Check: Measurement of hemoglobin concentration, blood pressure, and pulse.

4. Physician Examination: A final evaluation performed by a qualified physician, including auscultation of the heart and lungs, to determine final eligibility for donation.

Data Collection and Analysis

De-identified data were extracted from the Institute's electronic database. Variables included donor demographics (age, gender, residence), donor status (first-time vs. repeat), and documented reasons for temporary or permanent deferral. Data analysis was performed using Microsoft Excel. Descriptive statistics were used to summarize the dataset. Categorical variables (e.g., deferral reasons, gender) were expressed as frequencies and percentages, whereas continuous variables (e.g., age) were described using mean and standard deviation. Associations between categorical variables – including gender, donor status, and deferral reasons – were examined using the Chi-square (χ^2) test of independence. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

As the study utilized pre-existing, anonymized programmatic data, informed consent was waived. The study protocol adhered to the principles of the Declaration of Helsinki and received approval from the institutional ethics committee (Approval No. 12-09/2025).

Results

During the study period, a total of 15,791 individuals presented for voluntary blood donation. Of these, 13,834 (87.61%) were eligible and successfully donated blood, while 1,957 (12.39%) were deferred based on established criteria.

Demographic Characteristics of Deferred Donors

Among the 1,957 deferred individuals, 56.41% were male and 43.59% were female. Ages ranged from 18 to 65 years, with a mean age of 37.03 ±13.02 years. The highest portion of deferrals occurred in the 18-25 age group (497 donors, 25.40%), followed by the 36-45 age group (481 donors, 24.58%). A detailed age distribution is provided in **Table 1.**

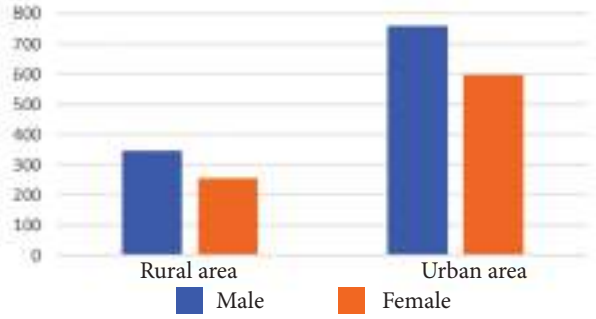
Most deferred donors resided in urban areas (1,356 donors, 69.29%), whereas 600 (30.66%) were from rural areas (**Graph 1).**

Table 1. Demographic characteristics of deferred blood donors

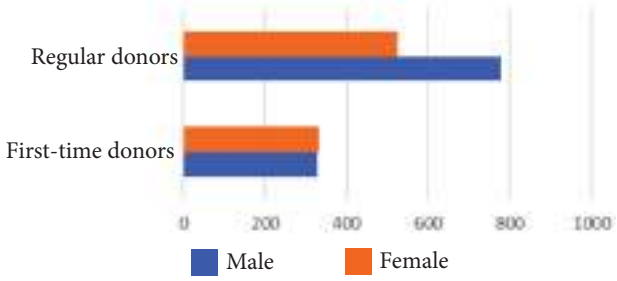
Age Group (Years)	Male	%	Female	%	Total	%
18-25	196	10.02	301	15.38	497	25.40
26-35	256	13.08	169	8.64	425	21.72
36-45	286	14.61	195	9.96	481	24.58
46-55	231	11.80	122	6.23	353	18.04
>56	135	6.90	66	3.37	201	10.27
Mean Age	39.05		34.40		37.03	
Standard Deviation	±12.70		±12.97		±13.02	

Table 2. Frequency of temporary and permanent blood donor deferrals

Type of Deferral	Male	%	Female	%	Total	%
Temporary	1,020	52.12	788	40.27	1,808	92.39
Permanent	84	4.29	65	3.32	149	7.61



Graph 1. Demographic characteristics of deferred donors by place of residence



Graph 2. Distribution of deferred donors by donor status

Donor Status and Type of Deferral

Repeat donors accounted for the majority of deferrals (1,302 donors, 66.53%), while first-time donors represented 655 (33.47%) of deferred individuals (**Graph 2**). Most deferrals were temporary (1,808 donors, 92.39%), while permanent deferrals comprised 149 cases (7.61%) (**Table 2**).

A Chi-square analysis showed no statistically significant association between gender and deferral type ($\chi^2 = 0.00$, df = 1, $p = 1.00$), indicating that males and females were similarly represented among temporary and permanent deferrals.

Reasons for Donor Deferral

The distribution of deferral causes is shown in **Table 3**. The most common reason for deferral was low hemoglobin, accounting for 706 cases (36.08% of all deferrals). This reason was significantly more frequent in women (20.64%) than in men (15.43%). A Chi-square test confirmed a strong association between gender and low hemoglobin deferral ($\chi^2 = 359.44$, df = 1, $p < 0.001$).

Medication use was the second most common cause (347 donors, 17.73%). Acute infections accounted for 225 deferrals (11.50%). Chronic diseases – primarily bronchial asthma and Hashimoto's thyroiditis – were the leading cause of permanent deferral, affecting 149 donors (7.61%). Other notable deferral reasons included risky behaviors (71 donor, 3.63%), hypotension (50 donors, 2.55%), and hypertension (50 donors, 2.55%).

Discussion

Ensuring a safe and adequate blood supply requires transfusion services to maintain a delicate balance between rigorous donor screening and the preservation of a sufficient donor pool. The deferral rate observed in this study – 12.39% – highlights this challenge and aligns closely with findings from Pakistan (12.9%) and several Southeast Asian countries, where rates range from 8.1% to 18.8% [2,7]. Such consistency across diverse settings underscores that donor deferral is an intrinsic component of blood collection systems worldwide. Although the specific causes vary by region, deferral patterns are shaped by local epidemiology, regulatory framework, and donor demographics [8–10].

One of the most notable finding in our study is the high portion of deferred donors in the 18-25 age group (25.40%). This pattern is widely reported internationally [2,5,6,11] and is particularly concerning because young donors form the foundation of a sustainable long-term blood supply. Deferral at a first donation attempt – often for temporary and reversible reasons – can discourage young individuals from becoming lifelong do-

Table 3. Criteria for temporary and permanent deferral of blood donors

Reason for Deferral	Male	%	Female	%	Total	%
Low hemoglobin levels	302	15.43	404	20.64	706	36.08
Medication use	239	12.21	108	5.52	347	17.73
Acute infections	157	8.02	68	3.47	225	11.50
Chronic diseases*	84	4.29	65	3.32	149	7.61
Risky behaviors**	51	2.61	20	1.02	71	3.63
Hypotension	11	0.56	39	1.99	50	2.55
Hypertension	33	1.69	17	0.87	50	2.55
Repeated serological testing	35	1.79	13	0.66	48	2.45
Recent surgery	27	1.38%	19	0.97%	46	2.35
Previous donation <12/16 weeks	29	1.48	11	0.56	40	2.04
Donor withdrawal	25	1.28	7	0.36	32	1.64
Tattoo/piercing	17	0.87	10	0.51	27	1.38
Menstruation	0	0.00	21	1.07	21	1.07
Insufficient body weight	0	0.00	13	0.66	13	0.66
Endoscopic procedures	9	0.46	4	0.20	13	0.66
Acupuncture	4	0.20	0	0.00	4	0.20
Recent vaccination	1	0.05	0	0.00	1	0.05
Other***	80	4.09	34	1.74	114	5.83

*Chronic diseases include bronchial asthma and Hashimoto's thyroiditis; ** Risky behaviors include: recent unprotected sexual contact with a new partner, history of sexually transmitted infections (STIs), multiple sexual partners, and intravenous drug use.; ***Other reasons include: travel to endemic areas, pregnancy termination, tooth extraction.

nors [6]. Thus, of the implications extend beyond a single missed donation and emphasize the need for targeted youth-centered donor engagement strategies.

Contrary to the common assumption that first-time donors are most frequently deferred, our data showed that established repeat donors accounted for the majority of deferrals (66.53%). This counterintuitive finding may be interpreted in two ways. On the one hand, it could reflect a highly effective pre-screening and education process for new donors. On the other, it highlights a key vulnerability within the donor pool: regular donors are more prone to transient health issues. Conditions such as temporary medication use, seasonal infections, or fluctuating hemoglobin levels – particularly among otherwise healthy and committed donors – represent a recurrent operational challenge. These findings shift the focus from recruitment alone to the proactive health monitoring and retention of existing donors, who constitute the most valuable and reliable component of the blood supply system.

Low hemoglobin emerged as the predominant cause of deferral in our study (36.08%), with a pronounced gender disparity affecting female donors. This is a near-universal finding, firmly established in the literature from India to Brazil [9,12–15]. Physiological factors associated with menstruation and childbirth, combined with nutritional iron deficiency, places women at increased risk [13]. This represents a clear opportunity for targeted intervention. Donor-centered health initiatives, including education on iron-rich diets and consideration of prophylactic iron supplementation for high-risk groups (particularly young women), could directly address this single largest barrier, converting a significant portion of temporary deferrals into successful donations [9,13]. In our study, gender was significantly associated with low hemoglobin deferral, reaffirming previous reports that female donors are more vulnerable to anemia-related deferrals. Conversely, no association was found between gender and the type of deferral. These findings suggest targeted nutritional support and screening for female donors could reduce avoidable deferrals and increase long-term donor retention.

Other common temporary deferral categories, such as medication use (17.73%) and acute infections (11.50%), further emphasize need for enhanced donor education. Many of these deferrals could be prevented through clearer communication of eligibility criteria, particularly regarding common over-the-counter medications and minor illnesses. Delivering this information in advance – through digital platforms, or informational leaflets – could empower donors to self-assess

and schedule donations appropriately, thereby reducing frustration and improving workflow efficacy [16].

The overwhelming predominance of temporary deferrals in this study (92.39%) is a highly encouraging finding, consistent with international data [17-20]. It demonstrates that the vast majority of deferred individuals are not permanently lost to the system and remain potential future donors. This highlights the critical importance of positive and informative deferral experience. A clear explanation of the deferral reason, respectful interaction, and specific guidance on when the donor may return are central to maintaining donor trust and willingness to return. This study should be interpreted in the light of its limitations. Additionally, as a single-center study conducted in the Vojvodina region, the findings may not be fully generalizable to other populations with different genetic, health, or socioeconomic profiles.

Conclusion

This study demonstrates that most blood donor deferrals arise from temporary and preventable health conditions, with low hemoglobin – especially among younger and female donors – representing the most frequent cause. The unexpected high proportion of deferrals among repeat donors underscores that donor retention requires more than recruitment alone; it demands meaningful donor engagement. To reduce avoidable deferrals and safeguard the donor pool, transfusion services must adopt a proactive approach: educate, pre-screen, and support. Perhaps most critically, the way deferred donors are treated today affects their willingness to return tomorrow. Every missed donation is an opportunity not just to restore supply, but to rebuild trust.

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CHARACTERISTICS AND TREATMENT OUTCOMES OF PATIENTS WITH SEVERE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

KARAKTERISTIKE I ISHOD LEČENJA BOLESNIKA SA TEŠKOM EGZACERBACIJOM HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA

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Abstract

Introduction. Chronic obstructive pulmonary disease is the fourth leading cause of death worldwide. Acute exacerbations often require hospitalization, and are associated with high mortality. Identifying risk factors associated with mortality may improve medical treatment and reduce mortality. This study aimed to analyze outcomes of patients with acute exacerbations of chronic obstructive pulmonary disease treated in the intensive care unit, and to identify factors associated with mortality. **Material and Methods.** This retrospective study was conducted at the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia, between April 2015 and January 2019. Inclusion criteria were a diagnosis of acute exacerbation of chronic obstructive pulmonary disease, intensive care unit admission, and treatment with invasive mechanical ventilation. **Results.** A total of 127 patients were included, of whom 79 (62.2%) were male, with mean age ($\overline{X}$ ± SD) of 66.96±8.57 years. Intensive care unit mortality was 33/127 (26%), with a mean length of stay of 3.5 days (interquartile range 2.0-8.0). Overall in-hospital mortality was 56/127 (44%), with a median hospital stay of 15.0 days (interquartile range 7.0-24.0). Multivariate analysis identified the PaO_2/FiO_2 ratio (odds ratio 0.99; 95% confidence interval 0.98-0.99; p=0.013), Glasgow Coma Score (odds ratio 0.82; 95% confidence interval 0.69-0.96; p=0.014), and presence of septic shock (odds ratio 50.9; 95% confidence interval 8.58-549.52; p< 0.001) as predictors of intensive care unit mortality. **Conclusion**. Mortality among patients with acute exacerbations of chronic obstructive pulmonary disease treated in the intensive care unit remains high. Reduced PaO_2/FiO_2 ratio, lower Glasgow Coma Score, and septic shock are independent predictors of mortality.

Key words: Pulmonary Disease, Chronic Obstructive; Symptom Flare Up; Risk Factors; Mortality; Intensive Care Units; Respiration, Artificial

Sažetak

Uvod. Hronična opstruktivna bolest pluća je četvrti vodeći uzrok smrtnosti u svetu. Akutne egzacerbacije bolesti često zahtevaju hospitalizaciju i značajno doprinose povećanju mortaliteta. Otkrivanje faktora rizika povezanih sa mortalitetom može doprineti boljoj terapiji bolesnika i smanjenju smrtnosti. Cilj rada bio je da se analizira ishod lečenja bolesnika sa akutnim egzacerbacijama hronične opstruktivne bolesti pluća u jedinici intenzivne terapije, kao i utvrditi faktore rizika za mortalitet kod ovih bolesnika. **Materijal i metode.** Studija je retrospektivnog karaktera. Sprovedena je na Institutu za plućne bolesti Vojvodine u Sremskoj Kamenici, Novi Sad, Srbija u periodu od aprila 2015. do januara 2019. godine. Uključujući kriterijumi su dijagnoza akutne egzacerbacije hronične opstruktivne bolesti pluća, prijem u jedinicu intenzivne terapije i lečenje invazivnom mehaničkom ventilacijom. **Rezultati.** Uključeno je 127 ispitanika, 79 (62,2%) muškog pola, prosečne starosti ($\overline{X}$ ± SD) 66,96 ± 8,57 godina. U jedinici intenzivne terapije mortalitet je iznosio 33/127 (26%) a prosečna dužina lečenja 3,5 dana (interkvartilni raspon 2–8), dok je bolnički mortalitet iznosio 56/127 (44%), a dužina lečenja 15 (interkvartilni raspon 7–24) dana. U multivarijantnoj analizi prediktori mortaliteta bili su odnos PaO_2/FiO_2 (odnos šansi, 0,99; 95% interval pouzdanosti, 0,98–0,99; p = 0,013), Glazgov koma skor (odnos šansi, 0,82; 95% interval pouzdanosti, 0,69–0,96; p = 0,014) i septički šok (odnos šansi, 50,9; 95% interval pouzdanosti, 8,58–549,52; p < 0,001). **Zaključak.** Mortalitet pacijenata sa akutnim egzacerbacijama hronične opstruktivne bolesti pluća lečenih u jedinici intenzivnog lečenja je visok. Niže vrednosti PaO_2/FiO_2, Glazgov koma skora i prisustvo septičnog šoka nezavisni su prediktori mortaliteta kod ovih pacijenata.

Ključne reči: hronična opstruktivna bolest pluća; egzacerbacija; faktori rizika; mortalitet; jedinica intenzivnog lečenja; mehanička ventilacija

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, progressive respiratory disorder characterized by persistent airway inflammation and incompletely reversible airflow limitation [1]. It results from an abnormal inflammatory response of the lungs to inhaled noxious particles or gases and remains a major global health burden [2]. According to the World Health Organization, COPD was the fourth leading cause of death worldwide in 2021, accounting for approximately 5% of all global mortality [3]. Na-

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Abbreviations

COPD – chronic obstructive pulmonary disease
AECOPD – acute exacerbation of chronic obstructive pulmonary disease
ICU – intensive care unit
FEV_1 – forced expiratory volume in one second
ICD – international disease classification
IQR – interquartile range
OR – odds ratio
CI – confidence interval
PaO_2 – partial pressure of oxygen in arterial blood
$PaCO_2$ – partial pressure of carbon dioxide
FiO_2 – fraction of inspired oxygen
CVI – cerebrovascular insult
TIA – transient ischemic attack
CAT – COPD Assessment Test
mMRC – modified Medical Research Council dyspnoea scale
MAP – mean arterial pressure
CRP – C-reactive protein

tional epidemiological data from Serbia indicate that COPD affected 3.5% of the population in 2019, reflecting a modest decline compared with earlier estimates from 2006 (4.3%) and 2013 (4.5%) [4]. In some patients, COPD may be associated with anatomical airway variations, such as a saber-sheath trachea [5].

Acute exacerbations of COPD (AECOPD) are episodes of clinical deterioration marked by worsening dyspnea, cough, and sputum production that necessitates medical intervention and adjustment of therapy [6]. Beyond exacerbating respiratory symptoms, these events can precipitate or aggravate chronic comorbidities, particularly cardiovascular and cerebrovascular diseases [7]. AECOPD is most frequently triggered by viral or bacterial infections or exposure to air pollutants [2]. Recommended management strategies include bronchodilators, systemic corticosteroids, antibiotics, and oxygen therapy, while non-invasive or invasive mechanical ventilation is reserved for severe cases [8]. In addition to improving arterial oxygenation, supplemental oxygen has been shown to enhance cerebral oxygen delivery and neurovascular function, potentially influencing cognitive outcomes and reducing cerebrovascular risk in patients with COPD [9].

Acute exacerbations of substantially accelerates disease progression and are associated with increased morbidity, mortality, and prolonged hospital stays [12]. Approximately 10% of exacerbations require hospitalization [10], and among patients admitted to intensive care units (ICUs), post-discharge mortality remains high. Data describing outcomes in the most severe exacerbations and associated mortality determinants are still limited [13]. A previous study from the Institute for Pulmonary Diseases of Vojvodina reported that among patients who died within the first 24 hours of admission for AECOPD, the leading causes of death were heart failure (37%), pneumonia (28%), pulmonary embolism (21%), and COPD itself (14%) [10]. In the United States, a 2012 study demonstrated that patients may experience up to 16 episodes of respiratory symptom worsening within the first two years following COPD diagnosis, reflecting the recurrent nature of exacerbations [11].

Early recognition and prompt management of AECOPD confer several clinical benefits. Early treatment mitigates the immediate impact of exacerbation, slows subsequent symptom deterioration, and reduces the likelihood of rehospitalization [14]. Prompt therapeutic intervention has been associated with faster symptom resolution, improved health-related quality of life, and decreased hospital admission rates [15]. Frequent exacerbations contribute to accelerated decline in pulmonary function, as reflected by reductions in FEV_1 [16]. Long-term outcomes remain poor, with hospitalized patients with AECOPD demonstrating an 82% lower 15-year survival compared with the general population [17]. Moreover, management of moderate-to-severe exacerbations imposes a substantial economic burden on healthcare systems [18].

Despite the recognized impact of AECOPD, evidence identifying predictors of mortality in patients requiring intensive care remains limited, particularly in region-specific settings. Identifying clinical, physiological, and treatment-related factors associated with mortality is essential for improving prognostication, guiding therapeutic decisions, and optimizing the allocation of critical care resources.

The aim of this study was to analyze treatment outcomes in patients with severe COPD exacerbations admitted to the intensive care unit and to identify risk factors associated with mortality in this patient population.

Material and Methods

This retrospective study was conducted at the Institute for Pulmonary Diseases of Vojvodina, Novi Sad, Serbia, and included patients treated between April 2015 and January 2019. The study was approved by the Ethics Committee of the Institute for Pulmonary Diseases of Vojvodina.

The study included patients with AECOPD requiring invasive mechanical ventilation. Patients were identified through the electronic medical records of the intensive care unit (ICU). Eligibility was based on a diagnosis of COPD, defined according to ICD-10 codes J44.1, J44.8 and J44.9. AECOPD was defined as worsening of cough, sputum production, and dyspnea requiring intensified therapy, including systemic bronchodilators. Inclusion criteria were admission to the ICU due to AECOPD, and requirement of invasive mechanical ventilation. Exclusion criteria included

diagnosis of asthma, pulmonary fibrosis, obesity hypoventilation syndrome (Pickwickian syndrome), transfer from another hospital, ICU admission for a primary condition other than AECOPD with concomitant COPD, or absence of clinical criteria fulfilling the diagnosis of AECOPD. The data extracted from medical records included demographic characteristics, length of hospital and ICU stay, smoking history, laboratory parameters, blood gas analyses, comorbidities, complications, and clinical outcomes.

During the study period, 234 patients with a diagnosis of COPD were treated in the ICU. Of these, 36 patients who did not require invasive mechanical ventilation were excluded. An additional 71 patients were excluded because ICU admission was not related to an episode of AECOPD.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for skewed data. Categorical variables are expressed as counts and percentages. Comparison between survivors and non-survivors were performed using Student's t-test or the Kruskal-Wallis test for continuous variables, depending on data distribution, and the chi-square (χ^2) test for categorical variables. Variables demonstrating statistical significance in univariate analysis were entered into a multivariate logistic regression model to identify independent predictors of mortality. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant [19].

Results

The study cohort comprised 127 patients, of whom 79 (62.2%) were male, with a mean age of 66.96 ± 8.57 years. Overall, 92 patients (72.4%) were current or former smokers, with a median smoking exposure of 40.0 pack-years (IQR 30–61.25). The emphysematous phenotype of COPD was documented in 36 patients (28.35%). At the time of ICU admission, type II respiratory failure was present in 99 patients (77.95%). The median PaO_2/FiO_2 ratio was 157.88 (IQR 109.69–230.06). Non-invasive ventilation was initially applied in 83 patients (65.35%), while percutaneous tracheostomy was required in 26 patients (20.47%).

The most frequent concomitant diagnoses was pneumonia in 61 patients (45.03%), cardiac decompensation in 12 (9.45%), and pulmonary embolism in 7 (5.51%). Influenza infection was confirmed in 7 patients (5.51%). The median duration of invasive mechanical ventilation was 2.0 days (IQR 1.0–5.5) days. Median ICU length of stay was 3.5 days (IQR 2.0–8.0), while total hospital length of stay 15.0 days (IQR 7.0–24.0) days. ICU mortality was 33/127 (26%), while overall in-hospital mortality reached 56/127 (44%). No statistically significant difference was found between ICU mortality and length of ICU stay (p=0.06). Although a downward trend in hospital mortality was observed over the study period, this did not reach statistical significance (p=0.29).

Comparison between survivors and non-survivors identified several factors significantly associated with mortality. Non-survivors had a significantly lower PaO_2/FiO_2 ratio (median 113.06, IQR 82.1–192.76 vs. 173.44, IQR 123.38–237.25; p=0.004), and lower Glasgow Coma Scale (GCS) scores at admission (median 10, IQR 6–13.5 vs. 13, IQR 10–14; p=0.03). Septic shock was markedly more frequent among non-survivors (n=12 (36.36%) vs. n=2 (2.13%); p<0.001), as was acute renal failure (ARF) (n=10 (30.3%) vs. n=13 (13.83%); p=0.03) **(Table 1).**

In multivariate logistic regression analysis, independent predictors of mortality were identified as PaO_2/FiO_2 ratio (OR 0.99; 95% CI 0.98–0.99; p=0.013), GCS (OR 0.82; 95% CI 0.69–0.96; p=0.014), and the presence of septic shock (OR 50.9; 95% CI 8.58–549.52; p<0.001).

Discussion

In this study, we evaluated the clinical characteristics, treatment outcomes, and predictors of mortality among patients requiring invasive mechanical ventilation for acute exacerbations of chronic obstructive bronchopulmonary disease (AECOPD). Multivariate analysis identified three statistically significant independent predictors of ICU mortality: impaired oxygenation reflected by low PaO_2/FiO_2 ratio, decreased level of consciousness as measured by the Glasgow Coma Scale (GCS), and the presence of severe infection manifested as septic shock). These findings underscore the central prognostic importance of gas-exchange failure, neurological status, and infection severity in critically ill patients with AECOPD.

The ICU mortality rate in our cohort was 26%, with an overall in-hospital mortality of 44%. These rates exceed those reported in several earlier studies, where ICU mortality ranged from 13.3% to approximately 25% and hospital mortality from 11–33% [13,14,20–24]. However, our findings are comparable with more recent data reporting ICU mortality of 25% and 28-day mortality of 34% [13]. Variability across studies likely reflects differences in patient selection, disease severity, comorbidity burden, and healthcare system characteristics. Long-term outcomes reported in the literature further highlight the poor prognosis of this population, with mortality rates of 4.5% at 12 weeks post-discharge [25], 26.2%

Table 1. Risk factors for mortality in the intensive care unit

Variable	Deceased (N=33)	Survivors (N=94)	p-value
Age (years), mean ± SD	65.73 ± 8.75	67.39 ± 8.51	0.41
Male gender, n (%)	23 (69.7%)	56 (59.57%)	0.30
Female gender, n (%)	10 (30.3%)	38 (40.43%)	0.30
Non-invasive ventilation, n (%)	13 (39.39%)	70 (74.47%)	<0.001
Duration of invasive ventilation (days), median (IQR)	2.5 (0–5)	2 (1–6)	0.47
PaO_2 (kPa), median (IQR)	8.69 (6.61–9.76)	9.09 (6.54–12.03)	0.29
PaO_2/FiO_2 ratio, median (IQR)	113.06 (82.1–192.76)	173.44 (123.38–237.25)	0.004
$PaCO_2$ (kPa), median (IQR)	7.635 (6.28–9.40)	7.56 (5.92–9.23)	0.85
pH, median (IQR)	7.26 (7.12–7.36)	7.28 (7.22–7.35)	0.12
Hemoglobin (g/L), median (IQR)	118.0 (98–143.5)	130.0 (113.5–145)	0.10
Hematocrit, median (IQR)	0.38 (0.31–0.45)	0.39 (0.34–0.45)	0.47
Leukocytes (×10^9/L), median (IQR)	16.0 (9.5–19.65)	10.8 (8.5–16.18)	0.06
Eosinophils (×10^9/L), median (IQR)	0.1 (0.02–0.2)	0.1 (0.03–0.2)	0.53
CRP (mg/L), median (IQR)	47.8 (27.4–133.73)	56 (13.66–135.07)	0.80
Procalcitonin (ng/mL), median (IQR)	1.4 (0.22–3.64)	0.22 (0.08–1.3)	0.10
Fibrinogen (g/L), median (IQR)	3.6 (2.70–5.58)	4.15 (3.32–6.14)	0.31
GCS score, median (IQR)	10 (6–13.5)	13 (10–14)	0.03
Smoker or former smoker, n (%)	26 (78.79%)	66 (70.21%)	0.34
Pack-years, median (IQR)	37.5 (24.38–50)	40 (30–65)	0.23
Emphysema, n (%)	6 (18.18%)	30 (31.91%)	0.13
Pneumonia, n (%)	20 (60.61%)	41 (43.62%)	0.09
Pleural effusion, n (%)	4 (12.12%)	14 (14.89%)	0.69
Pulmonary embolism, n (%)	4 (12.12%)	3 (3.19%)	0.05
Acute myocardial infarction, n (%)	5 (15.15%)	12 (12.77%)	0.72
Heart failure, n (%)	1 (3.03%)	6 (6.38%)	0.46
Atrial fibrillation, n (%)	5 (15.15%)	6 (6.38%)	0.12
Arterial hypertension, n (%)	20 (60.61%)	64 (68.09%)	0.43
Coronary artery disease, n (%)	5 (15.15%)	10 (10.64%)	0.49
CVI/TIA, n (%)	2 (6.06%)	10 (10.64%)	0.43
Hyperlipidemia, n (%)	0 (0%)	2 (2.13%)	0.40
Liver disease, n (%)	1 (3.03%)	3 (2.96%)	0.59
Diabetes mellitus without complications, n (%)	1 (3.03%)	9 (9.57%)	0.42
Diabetes mellitus with complications, n (%)	2 (6.06%)	8 (8.51%)	0.42
Acute renal failure, n (%)	10 (30.3%)	13 (13.83%)	0.03
Septic shock, n (%)	12 (36.36%)	2 (2.13%)	<0.001
Chronic renal failure, n (%)	3 (9.09%)	6 (6.38%)	0.60
Influenza, n (%)	1 (3.03%)	6 (6.38%)	0.47
Charlson comorbidity index, median (IQR)	4 (3–5)	4 (3–5)	0.70
Duration of ICU stay (days), median (IQR)	2 (0–5)	4 (2–10)	0.003
Total hospital stay (days), median (IQR)	5 (2–9.5)	18.5 (11–27)	<0.001

IQR – interquartile range; PaO_2 – partial pressure of oxygen in arterial blood; $PaCO_2$ – partial pressure of carbon dioxide; FiO_2 – fraction of inspired oxygen; CRP – C-reactive protein; GCS – Glasgow Coma Scale; CVI – cerebrovascular insult; TIA – transient ischemic attack; ICU – intensive care unit.

at one year, and up to 64.3% at five years [26]. Although specific causes of in-hospital death were not evaluated in this analysis, the discrepancy between ICU and total hospital mortality likely reflects advanced age, substantial comorbidity burden (Charlson index 4.05 ± 1.42), and severity of underlying COPD. Formal assessment of COPD severity was not feasible due to the absence of spirometric data, as spirometry is contraindicated during AECOPD. Furthermore, symptom burden (CAT, mMRC) and prior exacerbation history were unavailable due to the retrospective study design.

Comorbidities were common in our cohort, with systemic hypertension (66.1%), bronchiectasis (21.3%), diabetes (15.7%), pulmonary hypertension (12.6%), and

coronary artery disease (11.8%) being most prevalent. This pattern is consistent with prior studies, including a large cohort of 606 COPD patients in which hypertension (63.4%) and diabetes (35.8%) were similarly frequent, while the same study reported higher prevalence of heart failure, coronary artery disease, and dyslipidemia compared with our findings [27]. Other recent work from China reported respiratory failure, hypertension, coronary disease, and chronic heart failure as the most frequent comorbidities [21], findings largely consistent with our results, although respiratory failure was evaluated in our cohort as a gas-exchange parameter rather than as a comorbidity. Similar comorbidity profiles were noted in a Shanghai cohort of post-ICU AECOPD patients [25].

While autopsy studies have identified heart failure and pulmonary embolism as major causes of death in AECOPD [10], these conditions were not common in our cohort and did not significantly influence mortality. A study from Taiwan identified longer hospitalization and ICU admission as mortality predictors [28]; however, ICU treatment was an inclusion criterion in our study, precluding its assessment as a prognostic factor. Length of stay did not emerge as a significant predictor of mortality, though the shorter length of stay observed among non-survivors likely reflects early death in the most critically ill patients.

Our findings regarding PaO_2/FiO_2 ratio, GCS, and septic shock as independent mortality predictors are consistent with the previous reports. Prior studies have identified systemic hypertension, pneumonia, sepsis, acute renal failure, hypoglycemia and elevated serum creatinine [23,29–35]. In contrast, systemic hypertension and pneumonia were not independent predictors in our analysis, and variables such as serum creatinine and blood glucose were not included. Age has been widely reported as a mortality predictor [14,22,31,36,37], although several studies – consistent with our findings – have demonstrated no significant association [30,38,39]. Admission hypercapnia was also not associated with increased mortality, in line with previous observations [22,31,34].

A 2020 study identified advanced age (>80 years), respiratory failure on admission, fever, leukocytosis, elevated serum creatinine, and MAP <65 mmHg as mortality predictors [39]. Leukocytosis and hypotension – clinical markers of sepsis – support the strong prognostic role of infection severity. In our cohort, septic shock emerged as a significant independent predictor of mortality, emphasizing the importance of early detection and aggressive management of infectious complications in patients with AECOPD.

Notably, 45% of patients were admitted with concomitant pneumonia. Differentiating AECOPD from pneumonia can be clinically challenging due to overlapping symptoms; however, all included patients met established criteria for AECOPD, with documented symptom worsening necessitating intensified bronchodilator therapy. The high prevalence of pneumonia and its association with septic shock underscore the clinical relevance of infectious complications. This is particularly important in the context of chronic inhaled corticosteroid use and increased pneumonia risk, especially in patients with low eosinophil counts [4].

This study has several limitations. Its retrospective design restricts causal inference and is associated with incomplete clinical data. COPD severity could not be assessed due to the lack of spirometric measurements, symptom scales, and exacerbation history. Additionally, variables such as vaccination status and long-term inhaled therapy could not be statistically analyzed, limiting insights into their potential prognostic relevance.

Conclusion

Mortality among patients with acute exacerbations of chronic obstructive pulmonary disease requiring invasive mechanical ventilation in the intensive care unit is high. The PaO_2/FiO_2 ratio, Glasgow Coma Score, and the presence of septic shock were identified as independent predictors of mortality. Careful assessment of these parameters at admission and during ongoing clinical management may improve risk stratification and support timely therapeutic decision-making.

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PARENT PERSPECTIVES ON ROBOTIC-ASSISTED GAIT TRAINING FOR CHILDREN WITH CEREBRAL PALSY – A CROSS-SECTIONAL STUDY

PERSPEKTIVE RODITELJA O ROBOTSKI POTPOMOGNUTOM TRENINGU HODA ZA DECU SA CEREBRALNOM PARALIZOM – STUDIJA PRESEKA

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Abstract

Introduction. Robotic-assisted gait training is a high-technology rehabilitation intervention that has gained increasing popularity over the past two decades. However, limited research has explored how the parents of children with cerebral palsy perceive this intervention. The aim of this study was to examine parents' perspectives on robotic-assisted gait training with regard to the child's experience, its effects on impairments, and functional activities. **Material and Methods**. A total of 24 participants, including 23 mothers of children with cerebral palsy, completed an online cross-sectional survey distributed via SurveyMonkey. The survey was administered two months after completion of 20 sessions of robotic-assisted gait training. **Results.** All parents (100%) reported that robotic-assisted training was an enjoyable experience for their child and highly valued the quality of communication between the therapist and the child. Parents observed improvements in self-confidence (79.17%), muscle endurance (79.16%), muscle flexibility (66.66%), and reduced muscle tightness (78.26%). Additionally, improvements were noted in standing posture (54.07%), the ability to walk longer distances (62.50%), functional activities in daily life (66.66%), and participation levels (75%). **Conclusion**. Parents perceived robotic-assisted gait training as an engaging intervention that positively influences physical health, self-confidence, and happiness. Improvements in motor activities, participation in daily life, and quality of life were observed following 20 sessions of robotic-assisted gait training.

Key words: Gait; Robotics; Exercise; Cerebral Palsy; Parents; Motor Skills; Quality of Life

Sažetak

Uvod. Robotski potpomognuti trening hoda je visokotehnološka intervencija koja je stekla popularnost u poslednje dve decenije. Međutim, postoji nedostatak istraživanja o tome kako roditelji dece sa cerebralnom paralizom doživljavaju robotski potpomognuti trening hoda. Cilj studije bio je da se sagleda perspektiva roditelja dece sa cerebralnom paralizom o uticaju robotskog treninga hoda na detetovo iskustvo, na telesna oštećenja i funkcionalne sposobnosti. **Materijal i metode.** Dvadeset četiri ispitanika, među kojima je bilo dvadeset tri majke dece sa cerebralnom paralizom, popunilo je upitnik. Studija preseka sprovedena je putem onlajn ankete (*SurveyMonkey*), dva meseca nakon završetka 20 terapija robotskog treninga hoda. **Rezultati.** Svi roditelji (100%) smatraju da je robotski trening hoda zabavna intervencija i visoko su ocenili komunikaciju između terapeuta i deteta. Roditelji su izvestili o poboljšanju samopouzdanja (79,17%), povećanoj mišićnoj izdržljivosti (79,16%), većoj fleksibilnosti mišića (66,66%) i smanjenoj ukočenosti mišića (78,26%). Takođe su uočili poboljšanje posture u stojećem položaju (54,07%), hodanje na duže udaljenosti (62,50%), povećane funkcionalne aktivnosti u svakodnevnom životu (66,66%) i veću participaciju dece (75%). **Zaključak.** Roditelji smatraju da je robotski potpomognuti trening hoda intervencija koja podstiče aktivno učešće, poboljšava fizičko zdravlje, samopouzdanje i sreću dece. Roditelji su primetili da nakon 20 treninga postoje poboljšanja u motoričkim aktivnostima, participaciji i kvalitetu života.

Ključne reči: hod; robotika; trening; cerebralna paraliza; roditelji; motorika; kvalitet života

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Introduction

Cerebral palsy (CP) is a non-progressive neurodevelopmental disorder affecting motor and sensory function due to brain lesions, and consequently impairing movement, posture, and gait [1]. Motor impairments are frequently accompanied by additional disturbances, including deficits in cognition, sensation, communication, perception, behavioral regulation, and musculoskeletal complications [2]. Due to its complexity, CP management requires a multidimensional, individualized approach with clearly defined functional goals.

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Abbreviations
CP – cerebral palsy
RAGT – Robotic-Assisted Gait Training
GMFCS – Gross Motor Function Classification System
ROM – range of motion
QOL – quality of life
ICF – International Classification of Functioning, Disability and Health

Parental involvement is a crucial component to effective rehabilitation for children with CP. A family-centered approach emphasized early engagement of parents in the rehabilitation process, including participation in therapeutic decision-making and consideration of parental perspectives [3]. Ongoing parent education and home exercise programs enable caregivers to recognize changes and monitor progress in their children. Active collaboration between healthcare professionals and parents has been shown to increase satisfaction with treatment outcomes for both therapists and families [4].

Robotic-assisted gait training (RAGT) is a high-technology rehabilitation intervention that supports the patient using adjustable robotic orthoses (exoskeletons) for each leg, a body weight support system, a treadmill, and a feedback screen [5,6]. A key feature of RAGT is the delivery of intensive, repetitive practice of physiological gait patterns [7–9]. The system integrates computer-controlled algorithms f with video-based feedback, encouraging active cognitive and motor engagement during training [10–12]. RAGT has demonstrated potential benefits, including improvements in gait speed and endurance, stride length, cardiovascular fitness, balance, lower-limb muscle strength, motor planning, and other physiological functions [9,10,13]. Some studies suggest that RAGT may be more effective than conventional therapy improving gait speed, walking distance, and complex locomotor skills such as running and jumping in children with CP [11]. Despite the controversial results, scientific evidence does not clearly demonstrated superiority of RAGT over conventional therapies as it is generally considered an adjunct rather than a replacement for conventional physiotherapy [14–17].

Most existing research on RAGT has focused primarily on motor outcomes assessing standardized clinical measures [6,18–21]. In contrast, relatively few studies have explored the impact on quality of life (QOL) and daily functioning. A meta-analysis has suggested that RAGT may improve quality of life in adults with neurological impairments [22]. However, data addressing parent-reported outcomes related to QOL and daily life participation of children with CP remain limited. Given that parents are the primary caregivers and are often best positioned to observe subtle changes in their child's function, behavior, and participation, their perspectives are particularly valuable. Therefore, the aim of this study was to explore parental perspectives on the effects of RAGT, used as an adjunct to conventional physiotherapy.

Material and Methods

This cross-sectional survey study was conducted at the Zayed Authority for People of Determination, Abu Dhabi, UAE. Ethical approval was obtained from the Ethics Committee of Fatima College of Health Sciences, Abu Dhabi (INTSTF018PHY20). The study population consisted of parents of 26 children with CP who completed 20 RAGT sessions (five sessions per week, each lasting 40 minutes) using the Lokomat® system (Hocoma AG, Volketswil, Switzerland).

The survey was developed in English based on the International Classification of Functioning, Disability and Health (ICF) framework. It comprised five sections, beginning with information about the study purpose, informed consent, and parent demographics, followed by 20 survey items. Of these, 18 were mandatory closed-ended questions and 2 were optional open-ended questions that allowed parents to express positive or negative views regarding RAGT. The closed-ended questions addressed five domains: child behavior, impairments, mobility, participation, and quality of life. Responses were recorded using a five-point Likert scale. For analysis, responses of "strongly agree" and "agree" were classified as positive, "strongly disagree" "disagree" as negative, and "neutral" as neither positive nor negative. The final section of the survey thanked participants for their time and contribution.

The survey was reviewed by two pediatric rehabilitation researchers, who confirmed its conceptual framework and suggested minor revisions. The finalized version was translated into Arabic and distributed via SurveyMonkey through the therapy center. Survey links were sent to parents' mobile phones, and oral instructions regarding completion were provided. Data collection took place between May and July 2021. Parents were given up to eight weeks to complete the survey, with two reminder messages sent four weeks after initial distribution.

Closed-ended survey responses were analyzed using descriptive statistics. Open-ended responses were analyzed using qualitative content analysis to identify core themes and summarize parental perspectives. Representative quotes were selected and included in the Results section.

A total of 26 children completed the RAGT program, with a mean age of 7.69 ± 2.90 years. Of these, 61.5% were boys and 38.5% were girls. Bilateral cerebral palsy was present in 73.1% of the children, while

Table 1. Characteristics of children who completed Robotic-Assisted Gait Training

	n (%)/mean ± sd
Age	7.69±2.90
<6	8 (30.8%)
6-11.9	14 (53.8%)
12+	4 (15.4%)
Gender male	16 (61.5%)
Form	
Diplegia	13 (50%)
Hemiplegia	7 (26.9%)
Quadriplegia	3 (11.5%)
Mix	2 (7.7%)
Triplegia	1 (3.8%)
GMFCS level	
I	2 (7.7%)
II	8 (30.8%)
III	7 (26.9%)
IV	9 (34.6%)

Results are presented as mean ± sd or count (%)

26.9% had a unilateral form. According to the Gross Motor Function Classification System (GMFCS) [22], 61.5% of the children had moderate to severe CP, classified as levels III–IV (26.9% at level III and 34.5% at level IV), whereas 38.5% had mild impairment at levels I–II (7.7% at level I and 30.8% at level II). Detailed participant characteristics are presented in **Table 1.**

Results

The survey was completed by 24 parents, while 2 did not respond despite reminder messages. Participation was voluntary and responses were anonymous; therefore, the reasons for non-response could not be determined. Parental education levels were as follows: 10 parents held a university degree, 3 had vocational training, 7 had completed high school, 2 had elementary education, and 2 did not provide this information **(Table 2).**

The results are presented in five sections corresponding to the survey domains: child behavior, impairments, mobility, participation, and quality of life. Responses to the first 18 closed-ended questions are summarized in **Tables 3–6.** Findings from the open-ended question are presented separately.

As shown in **Table 3**, 23 parents (100%) responded to the question regarding the entertainment value of RAGT, with all respondents rating it positively; one parent did not answer this item. All 24 parents (100%) expressed a positive perception of communication between the therapist and the child. Regarding active participation and motivation to earn points through video games during RAGT, 21 parents (87.5%) reported positive responses, while 3 (12.5%) selected a neutral response. A positive change in the child's confidence and self-esteem was reported by 19 parents (79.2%), whereas 5 (20.8%) expressed no clear opinion. Perceptions of training intensity varied: 11 parents (45.8%) viewed the level of tiredness during or after sessions negatively, 9 (37.5%) perceived it positively, and 4 parents (16.7%) reported neutral responses.

Impairments

Overall, parents reported favorable effects of RAGT on physical impairments. Increased lower-limb strength and endurance were observed by 19 parents (79.2%),

Table 2. Parental Education Levels

Education Level	Number/% of Parents
University degree	10 (41.7%)
Vocational education	3 (12.5%)
High school	7 (29.2%)
Elementary school	2 (8.3%)
No response	2 (8.3%)

n = number of participants; % = percentage of total respondents

Table 3. Child's behavior domain

Questions	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Positive attitude	Negative attitude
1. Your child has fun while being part of the RAGT research project.							
	13 (54.17%)	10 (41.67%)	0%	0%	0%	23 (100%)	0%
2. Your child was excited about Lokomat training and the video games challenges.							
	13 (54.17%)	8 (33.33%)	3 (12.50%)	0%	0%	21 (87.50%)	0%
3. Your child communicates well with therapists during the RAGT sessions.							
	15 (62.50%)	9 (37.50%)	0%	0%	0%	24 (100%)	0%
4. Your child shows more self-confidence after RAGT sessions.							
	4 (16.67%)	15 (62.50%)	5 (20.83%)	0%	0%	19 (79.17%)	0%
5. Your child feels tired and complain during and after RAGT session							
	3 (12.50%)	6 (25%)	4 (16.67%)	8 (33.33%)	3 (12.50%)	9 (37.50%)	11 (45.83%)

n = number of participants; % = percentage of total respondent

while 3 parents (12.5%) were neutral and 2 parents (8.3%) reported no improvement. Improvements in trunk strength were noted by 13 parents (54.2%), with 9 parents (37.5%) selecting neutral responses and 2 parents (8.3%) disagreeing. Greater range of motion in the lower extremities was reported by 16 parents (66.7%), compared with 7 parents (29.2%) who were neutral and 1 parent (4.2%) who disagreed. A reduction in spasticity was observed by 19 parents (79.2%), while 4 parents (17.3%) were neutral and 1 (4.2%) disagreed. These findings are summarized in **Table 4.**

Mobility

Responses related to postural control and mobility are summarized in **Table 5.** Improvement in standing stability were reported by 12 parents (50%), while 10 parents (41.7%) were neutral, and 2 parents (8.3%) reported no change. Similar findings were observed for standing posture, with 13 parents (54.2%) noting improvement, 9 parents (37.5%) reporting neutral responses, and 2 parents (8.3%) reporting no improvement. Regarding walking distances, 15 parents (62.5%) observed longer walking durations following RAGT, 4 parents (16.7%) were neutral, and 5 parents (20.8%) reported no improvement. Improvements in balance and leg positioning were reported by 14 parents (58.3%), while 7 parents (29.2%) were neutral and 3 parents (12.5%) disagreed. Standing or walking as the preferred motor behavior was perceived by 13 parents (56.5%), with 8 parents (34.8%) selecting neutral responses and 2 parents (8.7%) disagreeing. Improvements in motor functions, such as standing up from a chair, picking up objects, and climbing stairs, were reported by 15 parents (66.7%), while 7 parents (29.2%) were neutral and 1 parent (4.2%) disagreeing.

Participation and quality of life

Within the participation domain, 18 parents (75%) reported increased social interaction at home and with peers, while 5 parents (20.8%) were neutral and 1 parent (4.2%) disagreed. Sustained effects two months after completion of RAGT were reported by 17 parents (73.9%), while 5 parents (20.1%) were neutral; one parent did not respond to this item. Improvements in quality of life were reported by 16 parents

Table 4. Impairment domain

Questions	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Positive attitude	Negative attitude
6. Your child become stronger (increased muscle strength and muscle endurance) on the lower limb after RAGT, compared to before the sessions.							
	5 (20.83%)	14 (58.33%)	3 (12.50%)	1 (4.17%)	1 (4.17%)	19 (79.16%)	2 (8.34%)
7. Your child become stronger (increased muscle strength and muscle endurance) in the trunk after the RAGT sessions.							
	3 (12.50%)	10 (41.67%)	9 (37.50%)	1 (4.17%)	1 (4.17%)	13 (54.17%)	2 (8.34%)
8. Your child has increased range of motions (mobility) in the hip, knee and ankle after RAGT compared with before.							
	5 (20.83%)	11 (45.83%)	7 (29.17%)	1 (4.17%)	0%	16 (66.66%)	1 (4.17%)
9. Your child has less spasticity (stiffness, tightness) in their lower legs after the RAGT sessions.							
	4 (17.39%)	15 (60.87%)	4 (17.39%0	0%	1 (4.35%)	19 (79.17%)	1 (4.35%)

n = number of participants; % = percentage of total respondents

Table 5. Mobility domain

Questions	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Positive attitude	Negative attitude
10. Your child is able to stand for a longer time (independently or with assistance) compared to before.							
	3 (12.50%)	9 (37.50%)	10 (41.67%)	1 (4.17%)	1 (4.17%)	12 (50%)	2 (8.34%)
11. Your child is able to stand with better posture (independently or with assistance) afterwards.							
	4 (16.57%)	9 (37.50%)	9 (37.50%)	1 (4.17%)	1 (4.17%)	13 (54.17%)	2 (8.34%)
12. Your child is able to walk longer distances (independently or with walker) after the sessions compared to before.							
	5 (20.83%)	10 (41.67%)	4 (16.67%)	4 (16.67%)	1 (4.17%)	15 (62.50%)	5 (20.84%)
13. Your child is able walk with better balance and better leg positioning (independently or with a walker) after the RAGT compared to before.							
	4 (16.67%)	10 (41.67%)	7 (29.17%)	3 (12.50%)	0%	14 (58.34%)	3 (12.50%)
14. Your child prefers standing or walking (independently or with walker) after the sessions in your home compared to before.							
	3 (13.04%)	10 (43.48%)	8 (34.78%)	2 (8.70%)	0%	13 (56.52%)	2 (8.70%)
15. Your child shows more motor activity in their daily life compared to before.							
	5 (20.83%)	11 (45.83%)	7 (29.17%)	1 (4.17%)	0%	15 (66.66%)	1 (4.17%)

n = number of participants; % = percentage of total respondents

Table 6. Participation and quality of life domain

Questions	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Positive attitude	Negative attitude
16. Your child shows more participation while engaging with family or friends compared to before the RAGT sessions.							
	5 (20.83%)	13 (54.17%)	5 (20.83%)	0%	1 (4.17%)	18 (75%)	1 (4.17%)
17. A positive benefit for your child is seen a few months after finishing the RAGT sessions.							
	4 (17.39%)	13 (56.52 %)	5 (20.09 %)	0%	0%	17 (73.91%)	0%
18. Has the quality of life improved for your child after they participated in the RAGT sessions? (Energy, tiredness).							
	8 (33.33%)	8 (33.33%)	7 (29.17%)	1 (4.17%)	0%	16 (66.66%)	1 (4.17%)

n = number of participants; % = percentage of total respondents

(66.7%), particularly related to increased energy levels and reduced fatigue. Seven parents (29.2%) reported neutral responses, and 1 parent (4.2%) disagreed. Findings are summarized in **Table 6.**

No negative comments regarding RAGT were reported. Three parents provided responses to the open-ended question describing positive experiences.

A parent of a child classified as GMFCS level IV stated: "*We noticed that our son is happier, and from the first week of RAGT we observed changes. Before RAGT, he mainly moved by crawling and could only take a few steps with our support. After the treatment, he is much more interested in walking and can now take more steps. It is now easier and quicker to change his diaper and to dress or undress him. We would love to repeat RAGT.*"

A parent of a child classified as GMFCS level III reported: "*My daughter stands more stably and walks longer with a walker after robotic treatment. We noticed that spasticity, especially in the calf muscle, has decreased. We would really like the robotic rehabilitation to continue.*"

A parent of a child who progressed from GMFCS level II to level I after the study shared: *"My daughter always wanted to walk in high-heeled shoes, but due to balance issues she couldn't. After the study, she managed to do it and is very happy. She can now climb stairs independently, safely, and quickly without support."*

Discussion

Robotic-assisted gait training (RAGT) has been used for nearly two decades as an adjunct therapeutic modality for children with cerebral palsy (CP). Incorporating parents' perspectives provides valuable insight into the translational benefits of RAGT, extending beyond objective gait parameters or standardized clinical outcomes. Parents' positive perceptions may reflect the value placed on even minimal improvements, which are considered meaningful in CP, where progression is typically slow or static after early childhood. However, qualitative and parent-centered research exploring perceived effectiveness of RAGD

remains limited. In a study by Beveridge et al., parents described RAGT as a revolutionary, inspiring, and safe intervention, valuing its effects on balance, motor function, and ambulation, although uncertainty remained regarding the transfer of these improvements into daily functional tasks [1].

In our study, all parents highlighted the entertaining nature of RAGT, particularly the integrated video-game components. The video-game interface appeared to enhance motivation by promoting active participation [2]. The platform's graded progression, from simplified tasks suitable for children with cognitive impairments to more complex game levels, allowed individualized challenge and sustained interest [24]. Children often identified with game characters or imagined themselves as robots, further increasing their enthusiasm for therapy [1]. The simultaneous motor and cognitive demands of RAGT may promote motor learning through intensive, repetitive, and task-oriented practice, thereby facilitating neuroplasticity [3,4]. Supporting this, Fu et al. demonstrated superior improvements in walking ability when virtual reality was combined with RAGT [24]. Parents in our study also emphasized effective communication between the therapist and the child. Verbal encouragement was perceived as a key factor motivating children to increase walking speed and improve performance in video games [2,5]. Although RAGT reduces the physical burden on therapists, individualized adjustment of gait parameters remains essential. In the absence of standardized protocols, parameter selection relies heavily on clinical expertise, and continuous supervision with verbal reinforcement is required [1,3]. Improvements in children's self-confidence reported by parents in our study align with findings by Pool et al., who observed positive effects on emotional health and sleep quality in children at GMFCS levels IV–V [6]. Nevertheless, the intensity of RAGT may contribute to fatigue. In our study, 37.5% of parents reported tiredness during or after sessions, likely related to the intensive schedule of five sessions per week over four consecutive weeks. Fatigue has been infrequently reported in the literature, although expert recommendations suggest that discomfort during early sessions – often related to harness strap pressure – is common but typically transient [7]. These findings underscore the importance of careful attention to patient fixation and comfort during early sessions.

Parents also reported increased flexibility, reduced stiffness, and improved muscle strength and endurance, with particular emphasis on enhanced lower-limb motion (ROM). These findings are consistent with previous studies suggesting that RAGT may positively influence joint flexibility. Djuric et al. observed improvements in ankle dorsiflexion, knee extension, and hip extension and abduction, although these changes did not reach statistical significance. Similarly, Žarković et al. reported increased hip extension and ankle dorsiflexion following a four-week RAGT program [25]. The use of elastic foot straps and harness during RAGT may facilitate stretching of spastic or tight muscles during the initial contact phase of the gait cycle, contributing to ROM gains. Although these changes may be small, they can still influence daily activities. Most parents also perceived a reduction in spasticity accompanied by improvements in muscle strength and endurance. However, evidence regarding the effects of RAGT on spasticity and muscle tone remains limited or inconclusive [26]. A systematic review and meta-analysis by Lim et al. highlighted the scarcity of direct measurements of muscle strength and spasticity a in RAGT studies [27]. Žarković et al. demonstrated reductions in excessive hip internal rotation, improved ankle dorsiflexion, and decreased abnormal muscle activity using three-dimensional kinematics and electromyography [28]. These findings suggest that RAGT can induce measurable changes in joint motion and muscle activation, complementing parent-reported functional improvements.

Walking was consistently valued by parents as a central component of their child's well-being. Beveridge et al. similarly reported parent-perceived improvements in walking speed, endurance, balance, toe clearance, and step length [1]. RAGT enables correction of gait deviations common in CP and supports the acquisition of more physiological gait patterns, including heel strike [9,10]. In non-ambulatory children, RAGT facilitated stable standing and supported walking, while in ambulatory children it contributed to longer walking durations and improved endurance. In our cohort, more than half of the parents reported improvements in standing, walking, and overall motor function, whereas fewer than 10% expressed negative perceptions regarding standing time, posture, or motor activities. Notably, 20.8% of parents did not report improvements in walking endurance. Nearly one-third of the children in our study were wheelchair users (GMFCS level IV), whose capacity for sustained standing and walking is inherently limited. For these children, RAGT nonetheless enabled prolonged walking compare with their baseline abilities, which often consisted of only a few steps with adapted walkers or manual assistance. While numerous studies have documented positive effects of RAGT on motor function, balance, and gait in children with CP across GMFCS levels I–IV [10–13], fewer have examined how these improvements translate into activities of daily living. Most RAGT studies include follow-up periods of three

to six months. Sustained benefits were reported by Cherni et al. up to six months after 24 RAGT sessions [10], and by studies in adolescents and adults showed maintenance of gains for up to four months [18]. Although not objectively measured, parents in our study reported sustained improvements for up to two months following completion of RAGT sessions.

Quality of life (QOL) is increasingly recognized as a critical outcome in CP research [19]. QOL reflects individual well-being across multiple domains and has been defined as the "value that an individual assigns to the duration of life as modified by impairments, functional states, perceptions, and social opportunities influenced by disease, injury, treatment, or policy" [20]. Numerous factors influence QOL in CP, including demographic, clinical, neuropsychological, psychosocial, financial, educational, and healthcare-related aspects [21,29]. Therefore, a holistic approach that addresses both physical and emotional needs is essential [30]. Motor function is a key determinant of QOL [31,32], although greater impairment does not necessarily equate to lower perceived QOL [31]. Blasco et al. reported higher parent-rated QOL and greater satisfaction with RAGT compared with conventional therapy [21], findings that align with the positive participations of participation and well-being reported by parents in our study. Although QOL was nor directly measured, indirect indicators such as energy expenditure and fatigue were included, and parents perceived improvements in these domains. Given is the chronic and non-progressive nature of CP, substantial changes in QOL are unlikely after a short intervention period, perceived improvements may reflect meaningful functional and emotional benefits.

Only three parents responded to the optional open-ended questions. Content analysis revealed that perceived benefits varies by GMFCS level: improvements in standing balance for children at level II, enhanced standing stability, longer walking with assistive devices, and reduced spasticity for level III, and increased motivation to walk, easier performance of daily activities, and improved mood for level IV. To our knowledge, such stratified qualitative observations have not been previously reported, limiting direct comparison with existing literature.

Conclusion

Most parents reported positive effects of robotic-assisted gait training on their child's active participation, motivation, and self-esteem. Perceived improvements in muscle endurance, flexibility, and reduced stiffness facilitated daily activities such as dressing and diapering. Parents particularly valued improvements in standing posture, walking endurance, participation in daily life, and the presence of benefits in the months following treatment.

This study has several limitations, including a relatively small sample size and unequal distribution by sex, age, Gross Motor Function Classification System level, and cerebral palsy subtype. The absence of objective measures of activities of daily living limits the ability to triangulate parent-reported outcomes. Future studies should integrate parental perspective with objective assessments of activities of daily living, muscle strength, and gait to strengthen the evidence base. Parental feedback provides important insight into the real-world impact of robotic-assisted gait training; however, combining subjective and objective measures is essential to fully understand and substantiate its functional benefits in children with cerebral palsy.

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QUALITY OF LIFE OF PATIENTS WITH PACEMAKERS

KVALITET ŽIVOTA PACIJENATA SA PEJSMEJKEROM

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Abstract

Introduction. Single-chamber and dual-chamber pacemakers are used for the treatment of bradycardia. Dual-chamber pacemakers more closely replicate physiological cardiac function by preserving atrioventricular synchrony, whereas single-chamber pacemakers are less complex, more cost-effective, and easier to implant. Clinical trials comparing these two pacing modalities have reported inconsistent results, largely depending on the studied population and study design. The AQUAREL questionnaire is a disease-specific instrument designed to assess life quality of life in patients with pacemakers. The aim of this study was to compare the quality of life of patients with single-chamber and dual-chamber pacemakers using the AQUAREL questionnaire. **Material and Methods.** After providing informed consent, 80 patients treated at the Institute for Cardiovascular Diseases of Vojvodina completed the AQUAREL questionnaire. Inclusion criteria were age ≥60 years and implantation of either a single or dual-chamber pacemaker. These criteria were met by 69 patients, including 33 with single-chamber and 36 with dual-chamber pacemakers. Data were obtained from the Institute's digital medical record. Statistical analysis was performed using standard methods. **Results.** The mean age of the patients was 76 years; 42 participants (63.77%) were male, and 92.75% had at least one comorbidity. Analysis of AQUAREL questionnaire scores revealed no statistically significant differences in overall quality of life between patients with single-chamber and dual-chamber pacemakers. **Conclusion.** Although patients with dual-chamber pacemakers reported fewer severe symptoms compared with those with single-chamber pacemakers, the difference was not statistically significant. Overall, no significant difference in quality of life was observed between patients according to pacemaker type.

Key words: Pacemaker, Artificial; Quality of Life; Surveys and Questionnaires; Signs and Symptoms

Sažetak

Uvod. Jednokomorski i dvokomorski pejsmejkeri se koriste za lečenje bradikardija. Dvokomorski pejsmejkeri teorijski nude više fiziološki pejsing zbog omogućavanja atrioventrikularne sinhronije, dok su jednokomorski jeftiniji i ugrađuju se brže. Brojna istraživanja koja su poredila navedene pejsmejkere su došla do različitih rezultata, u odnosu na ispitivanu populaciju i koncepciju istraživanja. AQUAREL je specifični upitnik za kvalitet života pacijenata sa pejsmejkerom, validiran je i preveden na više jezika. Cilj rada bio je poređenje kvaliteta života pacijenata sa jednokomorskim i dvokomorskim pejsmejkerom korišćenjem AQUAREL upitnika. **Materijal i metode.** AQUAREL upitnik je preveden na srpski jezik. Nakon potpisivanja saglasnosti, anketirano je 80 pacijenata koji su došli zbog redovne kontrole pejsmejkera u Institut za kardiovaskularne bolesti Vojvodine. Kriterijume za uključenje u studiju, koji podrazumevaju starost preko 60 godina i implantiran jednokomorski ili dvokomorski pejsmejker, ispunilo je 69, 33 sa jednokomorskim i 36 sa dvokomorskim pejsmejkerom. Iz baze podataka Instituta za kardiovaskularne bolesti Vojvodine prikupljeni su podaci o godištu pacijenta, vrsti pejsmejkera, kao i komorbiditetima. Podaci su obrađeni uobičajenim statističkim metodama. **Rezultati.** Prosečna starost ispitanika je 76 godina, 42 su muškog pola (63,77%), a 92,75% ima bar jedno pridruženo oboljenje. Rezultati dobijeni ispitivanjem putem AQUAREL upitnika pokazuju da ne postoji statistički značajna razlika (p = 0,493) u kvalitetu života ispitanika u odnosu na vrstu pejsmejkera. **Zaključak.** Bolesnici sa dvokomorskim pejsmejkerom prijavljuju manje izražene simptome u odnosu na bolesnike sa jednokomorskim pejsmejkerom, ali ta razlika ne dostiže nivo statističkog značaja, čime zaključujemo da nema razlike u kvalitetu života ispitanika u odnosu na tip pejsmejkera.

Ključne reči: pejsmejker; kvalitet života; upitnici i ankete; znaci i simptomi

Introduction

Pacemakers are implantable electronic devices used in the treatment of sinoatrial node dysfunction, atrioventricular (AV) block, reflex syncope, and hypertrophic obstructive cardiomyopathy. They are also indicated in selected cases following acute myocardial infarction and cardiac surgical procedures [1]. Single-chamber pacemakers sense and stimulate either the atrium or the ventricle, whereas dual-chamber pacemakers provide sensing and pacing in both chambers, thereby more closely replicating physiological cardiac activation. Rate-adaptive pacing refers to sensor-mediated adjustment of heart rate in re-

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Abbreviations

AV	– atrioventricular
VVIR	– ventricular pacing, ventricular sensing, inhibition response, rate-adaptive
DDDR	– dual pacing, dual sensing, dual response, rate-adaptive
ICVDV	– Institute for Cardiovascular Diseases of Vojvodina
ICD	– Implantable Cardioverter-Defibrillator

sponse to physical activity. Accordingly, pacing modes are designated as VVIR (ventricular pacing, ventricular sensing, inhibition response, rate-adaptive) for single-chamber pacemakers and DDDR (dual pacing, dual sensing, dual response, rate-adaptive) for dual-chamber pacemakers [2]. The expansion of indications for pacemaker implantation, along with population aging and increased life expectancy, has led to a steady rise in the number of pacemaker implantation procedures worldwide [3].

Epidemiological data from the United States indicate a pacemaker prevalence of 2.6 per 1,000 individuals, increasing markedly with age – from 0.4 per 1,000 among individuals aged 18–64 years to 26 per 1,000 in those older than 75 years. Pacemaker implantation is approximately 1.5 times more frequent in men [4]. In several European countries, the reported implantation rates during 2018-2019 ranged from 60 to more than 1,000 devices per million inhabitants [3].

Following pacemaker implantation, some patients may develop pacemaker syndrome, a clinical entity characterized by symptoms such as syncope, dyspnea, chest discomfort and pain, palpitations, and lethargy primarily resulting from AV dyssynchrony. The reported incidence of pacemaker syndrome in patients with VVIR pacing varies widely in literature, ranging from 7–10% as high as 83%. This variability is largely attributable to the absence of a universally accepted definition of pacemaker syndrome and nonspecific nature of its symptoms, which are common in cardiology patients regardless of pacemaker implantation. In addition to reducing the incidence of pacemaker syndrome, DDDR pacemakers are believed to lower the risk of atrial fibrillation, stroke, and mortality, while improving exercise tolerance and overall quality of life compared with VVIR pacemakers [2]. Notably, atrial fibrillation is associated with a more severe clinical course of hypertrophic obstructive cardiomyopathy [5].

The selection of pacemaker type is influenced not only by clinical evidence but also by practical and economic considerations. Single-chamber pacemakers are less expensive and simpler to implant and follow up, whereas dual-chamber devices preserve AV synchrony and more closely mimic physiological cardiac conduction [2]. British guidelines published in 1991 recommend atrial pacing in patients with preserved AV conduction and ventricular pacing in those with established or impending AV block.

Quality of life represents a critical clinical outcome encompassing physical, psychological, cognitive, and social dimensions. Although several generic quality-of-life questionnaires have been validated, they lack sufficient sensitivity for patients with pacemakers. To address this limitation, the AQUAREL questionnaire was developed as a disease-specific instrument for assessing quality of life in pacemaker recipients, with well-established psychometric properties and validated reliability [6].

Despite the theoretical advantages of DDDR pacing over VVIR pacing, the clinical benefits remain incompletely defined, particularly in the light of the substantially higher costs associated with dual-chamber systems [7]. Consequently, quality of life may represent an important additional parameter in the selection of pacemaker type [6].

The aim of this study was to compare the quality of life of patients with VVIR and DDDR pacemakers using the AQUAREL questionnaire.

Material and Methods

This prospective study was conducted at the Institute for Cardiovascular Diseases of Vojvodina (ICVDV), Novi Sad, Serbia, between December 2022 and January 2023. The study protocol was approved by the Ethics Committee of the Institute for Cardiovascular Diseases of Vojvodina in Sremska Kamenica, and all participants provided written informed consent prior to enrollment.

The AQUAREL questionnaire was translated into Serbian for the purposes of this study. The questionnaire consists of 24 items evaluating the frequency of symptoms commonly associated with pacemaker syndrome. A total of 80 patients presenting for routine pacemaker follow-up at ICVDV were screened. Inclusion criteria were age ≥60 years and implantation of either a single-chamber (VVIR) or dual-chamber pacemaker (DDDR) pacemakers. These criteria were met by 69 patients, of whom 33 had VVIR and 36 had DDDR pacemakers. Exclusion criteria included age <60 and implantation of an implantable cardioverter-defibrillator (ICD). Demographic and clinical data, including year of birth, pacemaker type, and comorbidities, were obtained from the ICVDV database. Data were analyzed using SPSS software, employing the Mann–Whitney U test.

Within the AQUAREL questionnaire, questions 1–6 assess chest discomfort; questions 7–12 evaluate dyspnea; question 13 assesses lower extremity edema; questions 14–16 assess palpitations; question 17 evaluates dizziness; question 18 explores difficulties in decision-making; question 19 examines memory impairment; question 20 assesses concentration; questions

Table 1. Patient comorbidities

Comorbidity	Group 1 (N=33)	Group 2 (N=36)	p-value
Arterial Hypertension	31 (93.93%)	31 (86.1%)	0.102
Atrial Fibrillation	23 (69.7%)	4 (11.11%)	<0.001
Type 2 Diabetes Mellitus	14 (42.42%)	5 (13.89%)	0.009
Valvular Heart Disease	20 (60.6%)	12 (30.56%)	0.024
Chronic Kidney Disease	5 (15%)	0 (0%)	0.016
Mean Age (years)	79	72.25	0.004
Mean Patient Response Score	1.11	1.007	0.493

Table 2. Comparison of symptom scores between patients with VVIR and DDDR pacemakers

Symptom	Group 1	Group 2	p-value
Dyspnea	0.35	0.4	0.839
Dizziness	0.51	0.7	0.622
Chest Discomfort	0.85	0.78	0.869
Palpitations	0.67	0.8	0.427
Insomnia	0.45	0.6	0.332
Reduced Sleep Quality	1.06	1.114	0.511
Decision-Making Difficulties	0.69	0.64	0.458
Memory	1.09	1.26	0.463
Concentration	1.06	1.083	0.626
Edema of Lower Extremities	1.21	1.22	0.92
Physical Activity	1.82	1.28	0.079
Fatigue	2.21	1.83	0.24
Overall Score	1.11	1.007	0.493

VVIR – ventricular pacing, ventricular sensing, inhibition response, rate-adaptive; DDDR – dual pacing, dual sensing, dual response, rate-adaptive.

21–22 evaluate insomnia and sleep quality; and question 24 addresses fatigue during daily activities. Physical activity tolerance is specifically assessed through questions 2-5, 8-10, and 23.

Results

The study population consisted of 69 participants, including 42 (60.9%) males, with a mean age of 76 years. Group 1 (VVIR pacemaker) included 33 patients, of whom 20 (60.6%) were male, with a mean age of 79 years. All patients in this group (n=33, 100%) had at least one comorbidity. Hypertension was present in 31 patients (93.93%), atrial fibrillation in 23 (69.7%), type 2 diabetes mellitus in 14 (42.42%), valvular heart disease in 20 (60.6%), and chronic kidney disease in 5 (15%) patients **(Table 1)**.

Group 2 (DDDR pacemaker) consisted of 36 participants, including 22 (61.1%) males, with a mean age of 72.75 years. Comorbidities were present in 31 patients (86.1%). Hypertension was observed in 29 patients (80.5%), atrial fibrillation in 4 (11.11%), type 2 diabetes mellitus in 5 (13.89%), and valvular heart disease in 12 (30.56%). None of the patients in this group had chronic kidney disease.

As shown in **Table 1**, statistically significant differences ($p<0.05$) were observed between the two groups regarding the prevalence of atrial fibrillation, type 2 diabetes mellitus, valvular heart disease, and chronic kidney disease. A statistically significant difference in mean age was also identified ($p=0.004$). These findings are consistent with current European Society of Cardiology (ESC) guidelines, which recommend VVIR pacemaker implantation in patients with atrial fibrillation and/or significant comorbidities.

Analysis of AQUAREL questionnaire responses revealed no statistically significant difference in overall quality of life between VVIR and DDDR pacemaker ($p=0.493$).

Mean symptom scores obtained from the questionnaire are presented in **Table 2**. Although patients with DDDR pacemakers demonstrated slightly better physical activity tolerance, this difference did not reach statistical significance.

Discussion

This study evaluated the quality of life of patients with single-chamber and dual-chamber pacemakers and demonstrated no statistically significant difference between the two groups based on pacemaker type.

Previous research by Nguyen et al. [8] showed that more than 70% of pacemakers are implanted in patients older than 70 years, suggesting that preservation of atrioventricular (AV) synchrony – achieved with dual-chamber (DDDR) pacemakers – may be particularly

beneficial in elderly patients [9,10]. A long-term Japanese observational study spanning 1979-2019 reported a 12.1-year increase in the mean age at first pacemaker implantation, especially among individuals aged over 80 and 90 years [11]. In line with these data, the mean age of patients in this present study was 76 years.

Dual-chamber pacemakers are associated with higher costs, greater implantation complexity, and an increased risk of complications compared with single-chamber devices [12]. Despite these differences, our analysis did not reveal statistically significant difference in overall quality of life between the two pacemaker types. Some subgroup analyses reported in the literature – notably in patients with sinus node dysfunction and AV block – suggest improved quality of life with DDDR pacemakers, particularly in terms of physical capacity and symptom burden [2]. Several retrospective studies have also reported improved clinical outcomes associated with dual-chamber pacing [13–15]; however, these findings are limited by selection bias, as DDDR devices are more frequently implanted in younger patients with fewer comorbidities. To minimize heterogeneity, this study included only patients older than 60 years. Nonetheless, statistically significant differences noted in **Table 1** must be considered.

Patients with DDDR pacemakers demonstrated a trend toward greater physical exertion capacity, although this did not reach statistical significance. This finding may be partially explained by the younger mean age and a lower prevalence of comorbidities – particularly atrial fibrillation – in this group. A meta-analysis of 14 studies comparing physical capacity in patients with single- and dual-chamber pacemakers reported inconsistent results: six studies showed significantly greater exertion capacity in DDDR patients, while eight found no difference between pacing modes [16]. Importantly, none of the included studies demonstrated inferior exertion capacity in patients with VVIR pacemakers. Variability in findings had been attributed to examiner bias and heterogeneous patient populations. Hemodynamic studies suggest that primary benefit of DDDR pacing during maximal exertion is mediated by rate responsiveness rather than AV synchrony alone [17].

Symptom analysis in the present study revealed no statistically significant differences between groups. Similar investigations have reported lower rates of dyspnea and reduced physical activity in VVIR recipients. This study evaluated 17 parameters, of which 11 showed a trend favoring DDDR pacemakers without reaching statistical significance, whereas 2 parameters – related to memory and concentration – demonstrated non-significant trends in favor of VVIR pacemakers [18]. Another comparable study reported left atrial enlargement and impaired left ventricular diastolic function associated with VVIR pacing [19]. Furthermore, Ouali et al. demonstrated significant increases in left atrial size (p=0.007) and pulmonary arterial pressure (p=0.0001) in patients with VVIR pacemakers, accompanied by worsening mitral regurgitation, which may contribute to a higher incidence of atrial fibrillation in this population [20].

This study did not assess perioperative complication rates. Data from the CTOPP trial (2000) showed a higher complication rate with dual-chamber pacemakers (9%) compared with single-chamber devices (3.8%) ($p < 0.01$) [21]. Large trials such as MOST [22] and UKPACE [23] found no superiority of DDDR pacing over VVIR in reducing stroke or mortality. The UKPACE trial evaluated the clinical benefits of single- versus dual-chamber pacemakers in elderly patients with AV block. The pacemaker type did not influence overall mortality over five years post-cardiac event or three years post-implantation, supporting the rationale for implanting DDDR devices in older patients [23]. Conversely, hemodynamic evidence suggests that atrial contribution to ventricular systolic function becomes increasingly important with advancing age [9,24] .

Patient perception of VVIR pacing may be influenced by prior exposure to DDDR pacing. Since pacemaker implantation – regardless of type – results in substantial improvement in quality of life compared with untreated AV block or sinus node disease, both groups experience marked benefit, making it difficult to determine which group perceives greater improvement [20].

Conclusion

No statistically significant difference in quality of life was identified between patients with dual-chamber and single-chamber pacemakers as assessed by the AQUAREL questionnaire **(Appendix 1)**. The cost of implantation should be taken into account when deciding between single-chamber and dual-chamber pacemakers.

Appendix 1. AQUAREL questionnaire

1. Have you felt discomfort in the chest? • no discomfort at all • very mild discomfort • mild discomfort • moderate discomfort • great discomfort	13. Did you have swollen ankles? • never • seldom • once in awhile • often • continuously

2. Do you get chest discomfort while walking upstairs or uphill? • no discomfort • very mild discomfort • mild discomfort • moderate discomfort • severe discomfort	14. Have you suffered from an irregular heartbeat? • never • seldom • once in awhile • often • continuously
3. Do you get chest discomfort while walking quickly on • • • level ground? • no discomfort • very mild discomfort • mild discomfort • moderate discomfort • severe discomfort	15. Have you suffered from heart pounding? • never • seldom • once in awhile • often • continuously
4. Do you get chest discomfort while walking on level ground at the same pace as people usually do at your age? • no discomfort • very mild discomfort • mild discomfort • moderate discomfort • severe discomfort	16. Have you suffered from pounding in the neck or abdomen? • never • seldom • once in awhile • often • continuously
5. Have you been restricted by chest discomfort during physical exercise? • Not restricted at all • Slightly restricted • Moderately restricted • Very restricted • Extremely restricted	17. Have you felt close to fainting? • never • seldom • once in awhile • often • continuously
6. Have you experienced chest discomfort at rest? • no discomfort • very mild discomfort • mild discomfort • moderate discomfort • severe discomfort	18. Have you noticed decision-making difficulties? • never • seldom • once in awhile • often • continuously
7. Do you get short of breath while walking upstairs or uphill? • not short of breath • very mildly short of breath • mild short of breath • moderate short of breath • extreme short of breath	19. Have you noticed memory fog? • never • seldom • once in awhile • often • continuously
8. Do you get short of breath while walking quickly on level ground? • not short of breath • very mildly short of breath • mild short of breath • moderate short of breath • extreme short of breath	20. Do you have difficulty to maintain focus? • never • seldom • once in awhile • often • continuously
9. Do you get short of breath while walking on level ground at the same pace as people usually do at your age? • not short of breath • very mildly short of breath • mild short of breath • moderate short of breath • extreme short of breath	21. Do you have trouble falling asleep? • never • seldom • once in awhile • often • continuously
10. Have you been restricted by breathlessness during physical exercise? • not restricted at all • slightly restricted • moderately restricted • very restricted • extremely restricted	22. Do you feel tired and exhausted after a night's sleep? • never • seldom • once in awhile • often • continuously
11. Have you been out of breath at rest? • not out of breath • slightly out of breath • moderately out of breath • very out of breath • extremely out of breath	23. Have you been restricted in your daily activities due to tiredness or lack of energy? • extremely restricted • very restricted • moderately restricted • slightly restricted • not restricted at all

12. Do you awake when sleeping due to shortness of breath? • never • seldom • once in awhile • often • continuously	24. Did you have to sit or lie down during the day to rest? • never • seldom • once in awhile • often • continuously

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QUALITY OF LIFE IN PATIENTS AFTER ACL RECONSTRUCTION WITH CONCOMITANT MENISCAL INJURY

KVALITET ŽIVOTA NAKON ARTROSKOPSKE MENISCEKTOMIJE I REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA KOLENA

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Abstract

Introduction. Anterior cruciate ligament injuries predominantly affect young, physically active, and working-age population. The objective of anterior cruciate ligament reconstruction extends beyond restoring knee stability and mechanical function; it also aims to improve the patient's overall quality of life. **Material and Methods.** A total of 307 patients diagnosed with anterior cruciate ligament injury were included in the study. This investigation builds upon our previous research, expanding the analysis to a larger patient cohort. Group A consisted of 187 patients with isolated anterior cruciate ligament rupture, while Group B included 120 patients with combined injuries: 70 with inner meniscus injuries, 24 with outer meniscus injuries, and 26 with injuries to both menisci. **Results and Discussion.** Analysis of the Knee Injury and Osteoarthritis Outcome Score revealed statistically significant differences across multiple parameters, including pain intensity, activities of daily living, sports and recreational function, and perceived quality of life. In all these domains, patients in Group A achieved better outcomes compared to those in Group B. Female patients demonstrated higher quality-of-life scores related to activities of daily living compared to male patients, which may be attributed to greater postoperative engagement in such activities. **Conclusion.** Although statistically significant differences were observed in several functional and quality-of-life domains, the overall findings did not demonstrate detectable clear advantage in quality of life for patients with isolated anterior cruciate ligament injuries compared to those with concomitant meniscal lesions following anterior cruciate ligament reconstruction.

Key words: Quality of Life; Anterior Cruciate Ligament Reconstruction; Meniscus; Wounds and Injuries; Knee

Sažetak

Uvod. Povrede prednjeg ukrštenog ligamenta najčešće pogađaju mlade, sportske i radno aktivne ljude. Cilj rekonstrukcije prednjeg ukrštenog ligamenta jeste ponovno uspostavljanje stabilnosti kolena i mehaničke funkcije; takođe cilj rekonstrukcije je i poboljšanje ukupnog kvaliteta života pacijenta. **Materijal i metode.** U istraživanje je ukupno uključeno 307 osoba sa dijagnozom povrede prednjeg ukrštenog ligamenta. Ono se nadovezuje na naše prethodne istraživačke napore, proširujući analizu na veću kohortu pacijenata. Grupa A se sastojala od 187 pacijenata koji su pretrpeli izolovanu rupturu prednjeg ukrštenog ligamenta, dok je B grupa obuhvatala 120 pacijenata: 70 sa povredama unutrašnjeg meniskusa, 24 sa povredama spoljašnjeg meniskusa i 26 koji su imali povrede oba meniskusa. **Rezultati i diskusija.** Analiza rezultata *Knee Injury and Osteoarthritis Outcome Score* upitnika za svaki parametar otkrila je relevantne razlike sa statističkom značajnošću u intenzitetu bola, svakodnevnim aktivnostima, učešću u sportu i percepciji kvaliteta života, gde je grupa A postigla bolje rezultate u poređenju sa grupom B. Žene su pokazale viši kvalitet života u odnosu na svakodnevne funkcionalne aktivnosti u poređenju sa muškarcima, verovatno zato što imaju tendenciju da više učestvuju u takvim aktivnostima nakon operacije. **Zaključak.** U našem istraživanju nismo identifikovali nikakvu uočljivu razliku koja bi ukazivala na to da osobe sa izolovanim rupturama prednjeg ukrštenog ligamenta imaju viši kvalitet života od onih koji imaju rupturu prednjeg ukrštenog ligamenta u kombinaciji sa lezijom meniskusa.

Ključne reči: kvalitet života; rekonstrukcija prednjeg ukrstenog ligamenta; meniskus; rane i povrede; koleno

Introduction

Injuries of the anterior cruciate ligament (ACL) predominantly affect young, physically active, and working-age individuals [1,2]. The reported annual incidence ranges from 30 to 78 cases per 100,000 individuals, while in high-risk populations – such as young athletes – the incidence may reach up to 85 cases per 100,000 in certain cohorts [3,4]. Previous studies have demonstrated considerably variability in the prevalence of concomitant injuries associated with ACL rupture, reporting 40-80% of patients with an ACL tear also sustain meniscal injury [5–7].

The primary objective of anterior cruciate ligament reconstruction (ACLR) extends beyond the restoration of knee stability and mechanical function; it also aims to improve patients' overall quality of life (QoL). In modern healthcare, patient-reported assessment of

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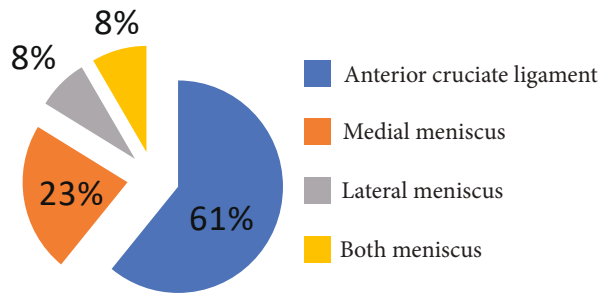
Abbreviations

ACL – anterior cruciate ligament
OA – osteoarthritis
PTOA – post-traumatic osteoarthritis
QoL – quality of life
WHO – World Health Organization
HRQoL – health-related quality of life
DLA – daily life activity
SD – standard deviation
AM – arithmetic mean
ACLR – anterior cruciate ligament rehabilitation
KOOS – Knee Injury and Osteoarthritis Outcome Score

health status are regarded as valid and essential indicators of well-being [8]. The World Health Organization (WHO) defines quality of life as an individual's subjective perception of their position in life within the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns [9]. Contemporary concepts of QoL increasingly emphasize subjective experience, moving away from exclusive reliance on objective or purely quantitative indicators. [10]. To assess QoL following arthroscopic ACLR, validated patient-reported outcome measures such as the ACL-QOL questionnaire and Knee Injury and Osteoarthritis Outcome Score (KOOS) are widely used [11].

The establishment of a clinical registry in 2012 at the Clinic for Orthopedic Surgery and Traumatology, University Clinical Center of Vojvodina in Novi Sad, enabled systematic investigation of postoperative outcomes and quality of life of patients with ACL injuries [12]. Through structured questionnaires, patients provide subjective evaluations of surgical outcomes and overall health status one year after ACLR [13]. The aim of the present study was to determine whether differences in quality of life exist between patients



Graph 1. Distribution of respondents based on concomitant injurie

with isolated ACL rupture and those with ACL rupture accompanied by concomitant meniscal injury – medial, lateral, or combined.

Material and Methods

This study was conducted at the Clinic for Orthopedic Surgery and Traumatology, University Clinical Center of Vojvodina, following approval from the institutional Ethics Committee. A total of 307 patients diagnosed with ACL rupture were included. The present investigation builds upon our previous research [14], expanding the analysis to a larger patient cohort. Participants were divided into two groups. Group A comprised 187 patients with isolated ACL rupture, while Group B included 120 patients with concomitant meniscal injury: 70 with inner meniscus injury, 24 with outer meniscus injury, and 26 with combined inner and outer meniscal injuries **(Graph 1).**

Statistical analysis revealed no significant differences between the groups regarding sex distribution, type of sport, level of sports activity, or limb laterali-

Table 1. Comparisons between groups based on various parameters

Parameters		Group A	Group B	Statistical significance
Gender	Male Female	145 42	97 23	p = 0.49 (>0.05) χ^2 = 0.46
Age	AM=26.3 min: 15 max: 55	AM =25.4	AM =27.6	p = 0.01 (<0.05)* t = 2.53
Type of sport activity	Professional Recreational Non-athletes	85 92 10	44 71 5	p = 0.11 (>0.05) χ^2 = 2.44
Level of sport activity	Recreational International Republican Regional Non-athletes	75 25 40 37 10	60 10 27 18 5	p = 0.07 (>0.05) t = -1.80
Laterality	Left Right Both	76 109 2	46 69 5	p = 0.83 (>0.05) χ^2=0.04
Time passed from injury to surgery	AM =10.2 months min: 1 month; max: 3 year	AM = 8.7 months	AM = 12.5 months	p = 0.001 (<0.05)* t=3.16

zation **(Table 1).** However, a statistically significant difference in age was observed, with patients in Group B being older on average than those in Group A (27.6 vs. 25.4 years). Additionally, the interval between injury and surgical intervention differed significantly, with patients in Group A undergoing ACLR earlier than those in Group B (8.7 months vs. 12.5 months, respectively).

Data collection was based on the KOOS questionnaire [15], supplemented with additional investigator-designed questions intended to obtain more detailed and comprehensive clinical information. These supplementary questions did not influence the final KOOS scoring or outcome interpretation [16]. The questionnaire consisted of five sections: (1) symptoms experienced by the patient; (2) pain during various physical activities; (3) activities of daily living (ADL); (4) physical activity level assessed in conjunction with the Lysholm Knee Scoring Scale; and (5) patient perception of overall quality of life and subjective understanding of the injury.

Prior to surgery, all participants completed a baseline questionnaire addressing injury characteristics and subjective symptoms. One year after ACLR, follow-up data were collected via email and/or telephone interviews, following prior patient notification and informed consent. All responses were anonymized and used exclusively for scientific analysis. Exclusion criteria included refusal to participate or continue participation, as well as failure to respond to email or telephone contact attempts.

Within the KOOS framework, scores range from 0 (extreme symptoms) to 100 (no symptoms). Due to the inclusion of supplementary questions, the scoring procedure deviated slightly from the standard KOOS protocol [12]; however, the resulting scores remained equivalent to those generated by the original scoring methodology.

The Lysholm Knee Scoring Scale is a validated patient-reported outcome measure used to assess knee-related symptoms and functional limitations [17]. It consists of eight items, yielding a total score ranging from 0 to 100, with higher scores indicating better knee function. The evaluated domains include limping (5 points), need for walking support (5 points), locking (15 points), instability or giving way (25 points), pain (25 points), swelling (10 points), stair climbing (10 points), and squatting ability (5 points) [17].

Descriptive statistical analyses included calculation of arithmetic mean (AM), standard deviation (SD), and minimum and maximum values for parametric variables. Frequencies were used to describe categorical variables. Comparative analysis between groups was performed using Student's t-test for parametric data and Pearson's χ^2 test for non-parametric variables.

Results

The mean preoperative Lysholm score was 76.26 in Group A and 69.69 in Group B. Postoperatively, Lysholm scores increased to 89.4 in Group A and 87.9 in Group B. No statistically significant differences were observed between the two groups in postoperative Lysholm scores. However, a significant difference was identified preoperatively, with Group A demonstrating markedly higher values Lysholm scores than Group B. In addition, both groups exhibited statistically significant improvements when comparing preoperative and postoperative values, with postoperative scores being substantially higher in each group **(Table 2).**

Analysis of the KOOS questionnaire results by individual subscales **(Table 3)** revealed statistically sig-

Table 2. Differences in Lyshol score between and within groups A and B

Lysholm score	t-test	p
Differences between groups in postoperative Lysholm score	-1.93	0.054 (>0.05)
Differences between groups in preoperative Lysholm score	-3.32	0.001 (<0.05)*
Differences within group A preoperative/postoperative	-10.58	0.000 (<0.05)*
Differences within group B preoperative/postoperative	10.41	0.000 (<0.05)*

Table 3. Assessment of quality of life based on the KOOS questionnaire

	Questionnaire in total (43 items)	Questionnaire scale				
		Subjective symptoms (6 items)	Pain intensity (6 items)	Daily life activities (DLA) (11 items)	Sport activities (14 items)	QoL awareness (6 items)
AM	107.25	16.40	10.38	19.45	45.82	15.18
SD	17.51	3.08	1.60	3.22	12.09	3.69
min	0	0	0	0	0	0
max	146	22	12	22	69	21

Table 4. Significance of differences on KOOS questionnaire scales according to injury type and gender

		Subjective symptoms	Pain intensity	Daily life activities (DLA)	Sport activities	QoL awareness
Injuries (LCA/LCA+ meniscal lesion)	t-test	-1.82	-2.23	-1.99	-2.04	-2.88
	p	0.06 (>0.05)	0.02 (<0.05) *	0.04 (<0.05)*	0.01 (<0.05) *	0.004 (<0.05) *
Gender (male/female)	t-test	-1.45	0.79	-1.21	-1.38	-2.09
	p	0.15 (>0.05)	0.43 (>0.05)	0.22 (>0.05)	0.17 (>0.05)	0.03 (<0.05) *

Table 5. Descriptive data on the significance of differences on KOOS questionnaire scales based on injury type and gender

	AM				SD			
	Injury		Gender		Injury		Gender	
	LCA	LCA+ meniscal lesion	M	F	LCA	LCA+ meniscal lesion	M	F
Subjective symptoms	16.64	15.99	16.26	16.88	2.98	3.17	3.04	3.15
Pain intensity	10.55	10.2	10.42	10.24	1.5	1.72	1.63	1.46
Daily life activities (DLA)	19.74	19.0	19.33	19.87	3.10	3.36	3.31	2.82
Sport activities	47.14	43.77	45.33	47.66	10.91	13.49	12.28	11.25
QoL awareness	15.66	14.43	14.95	16.03	3.38	4.02	3.70	3.52

nificant differences between the groups in pain severity, activities of daily living, sports and recreation, and subjective perception of quality of life **(Table 4).** In all these domains, Group A achieved significantly higher scores than Group B **(Table 5).** Furthermore, gender-based analysis demonstrated significant differences in quality of life perception, with female participants reporting higher levels of awareness compared with male participants **(Tables 4 and 5)**.

Discussion

Over the past five years, both the annual incidence of registered ACL injuries and the number of ACLR procedures performed have approximately doubled. The primary objectives of ACLR includes restoring knee stability, improving quality of life, preserving range of motion, and preventing progressive cartilage and meniscal degeneration, as well as reducing the risk of subsequent knee injuries. Facilitating patients' reintegration into everyday social life, returning to occupational duties, and resumption of athletic activity at pre-injury levels is particularly important given that ACLR is predominantly performed in younger individuals. From this perspective, systematic evaluation of postoperative outcomes is fully justified not only clinically but also socially [18,19].

Overall, postoperative quality of life following ACLR does not appear to be strongly correlated with patient age; however, specific questionnaire domains reveal meaningful differences. Women demonstrated higher quality of life related to activities of daily living than men, possibly reflecting greater engagement in such activities during the postoperative period. Patients in their forties appeared to cope better with postoperative symptoms than younger individuals, while men generally reported greater tolerance to postoperative pain than women. Younger patients, particularly those under 25 years of age, expressed greater satisfaction with sports participation compared with older cohorts [20].

It has been estimated that between 50% and nearly 100% of women sustaining an ACL injury will develop clinically significant pain, functional limitations, and radiographic evidence of knee osteoarthritis (OA) within 12-20 years [21,22]. The reported prevalence of concomitant meniscal injury in in ACL tears ranges from approximately 22% to 86% [23]. For decades, arthroscopic meniscectomy has been considered the standard treatment for meniscal lesions [23]. Although arthroscopic techniques provide advantages such as minimal invasiveness, faster recovery, and low complication rates, partial meniscectomy is nonetheless associated with an increased long-term risk of OA development [24]. Regardless of surgical technique, more than 50% of patients with ACL rupture exhibit clinical signs of knee OA within 15 years following surgery [25]. When ACL rupture is accompanied by meniscal injury, the likelihood of degenerative knee changes is even higher compared with isolated ACL tears [26].

Phillips et al. [27] reported that 10,001 participants (65%) had isolated ACL rupture, 2,895 individuals (18.8%) had concomitant medial meniscus injury, and 2,496 patients (16.2%) had lateral meniscus injury. Mortazavi et al. [28], in a longitudinal study of 111 patients with a mean follow-up of 23 months, found that the interval between injury and surgery was

longest in patients with medial meniscus damage (17.4 ± 16.8 months), followed by lateral meniscus injury (9.3 ± 8.3 months), and shortest in isolated ACL rupture (7.4 ± 8.1 months). A similar pattern was observed in our study, with considerably shorter time to surgery in patients with isolated ACL tears (8.7 months) compared with those with additional intra-articular injuries (12.5 months).

Functional outcomes in the present study were assessed using the Lysholm scoring scale [29]. Preoperatively, Group A demonstrated higher scores than Group B (76.26 vs. 69.69). Postoperatively, both groups showed marked improvement, with scores increasing to 89.4 and 87.9, respectively. While postoperative scores did not differ significantly between groups both, the postoperative disparity suggests greater functional impairment in patients with concomitant meniscal injury. These findings are consistent with those of Shoemaker et al. [30] who evaluated 1,228 patients with ACL injuries, including those with concomitant meniscal lesions, and analyzed changes in Lysholm scores before and after surgical treatment. In their cohort, patients with isolated ACL injuries had a mean preoperative Lysholm score of 61.0, which improved to 92.1 postoperatively. In contrast, patients with combined ACL and meniscal injuries demonstrated lower preoperative scores (mean 52.3), which increases to 90.1 following surgery.

Surgical reconstruction remains the preferred treatment for ACL rupture, particularly in young, physically active individuals and competitive athletes [1]. Consequently, optimal preoperative planning, precise surgical technique, and structured postoperative rehabilitation are essential for successful outcomes [31]. Approximately 83% of competitive athletes and 80% of recreational athletes return to sports following ACLR, although rates vary by sport [32–35]. Registry-based studies consistently demonstrate that ACLR results in improved quality of life, higher activity levels, and reduced subjective instability compared with conservative, non-operative management [33]. Psychological factors play a crucial role in postoperative recovery. Fear of reinjury, mental readiness, and self-confidence significantly influence return-to-sport outcomes [34]. Despite advances in surgical and rehabilitation strategies, the risk of secondary ACL rupture remains substantial, with reported rates ranging from 2% to 15% [16,18]. These injuries pose a considerable burden to patients and healthcare systems, contributing to long-term clinical and socioeconomic challenges.

Quality of life assessment – encompasses both subjective self-evaluation and objective external assessment. Numerous instruments have been developed to quantify health-related quality of life (HRQoL) [35,36]. Currently, HRQoL is recognized as central outcome measure in clinical practice and medical decision-making, serving as an important benchmark for patient outcomes and overall well-being [37]. Evaluating HRQoL and fear-avoidance beliefs in both uninjured athletes and those following ACLR provides valuable insight into targeted interventions [15].

The KOOS questionnaire was specifically designed to evaluate knee injuries with potential progression to post-traumatic osteoarthritis (PTOA) [16]. In our study, statistically significant differences were observed across all KOOS subscales except the QoL domain, with Group A achieving higher scores in pain, daily activities, and sports/recreation. Gender-based differences were also evident, with female patients demonstrating higher awareness and perception of quality of life. Similarly, Ulstein et al. [38] analyzed outcomes in 8,408 patients – 4,774 with ACL tears and 3,634 with concomitant meniscal injuries – and reported comparable mean KOOS scores between two groups across all subscales at a 5-year follow-up. Notably, patients with associated meniscal lesions exhibited greater improvement from baseline to the 5-year assessment in the pain, activities of daily living, and sports/recreation subscales. Cristiani et al. [39] evaluated KOOS outcomes in 5,378 patients and likewise reported no significant postoperative differences between patients with isolated ACL tears and those with concomitant meniscal injuries at either the 1-year or 2-year follow-up. However, significant preoperative differences were observed in the pain, daily activities, and sports/recreation subscales, with the lowest scores recorded in patients with lateral meniscus involvement. In contrast, Barenius et al. [40], in an 8-year prospective study of 164 patients, found that individuals with isolated ACL tears consistently achieved superior outcomes across all five KOOS subscales compared with those who sustained combined ACL and meniscal injuries.

The prevalence of PTOA after ACL injury has been reported to reach up to 87% [41]. Systematic reviews confirm a higher OA risk in patients with combined ACL and meniscal injuries, particularly with follow-up durations exceeding 10 years [15,38]. Once advanced OA develops, degenerative changes are largely irreversible, often leaving total knee arthroplasty as the only therapeutic option [41]. Severe OA is associated with pronounced reductions in HRQoL, emphasizing the substantial clinical burden of these injuries [42].

Although our 1-year follow-up did not demonstrate significant differences in overall QoL between groups, this does not preclude later deterioration.

Evidence indicates that at 5 years or more post-injury, radiographic OA changes are more prevalent in combined ACL-meniscus injuries and strongly associated with poorer QoL outcomes [34]. Advances in meniscal repair techniques may help reduce OA incidence in the future [43].

Several limitations should be acknowledged. First, reliance on subjective patient-reported outcomes may introduce reporting bias. Second, the relatively short follow-up period limits detection of early degenerative changes that may influence long-term quality of life. Clinical and self-reported assessments often show limited correlation, further emphasizing this limitation [20].

Overall, no significant association was identified between quality of life and age group when comparing younger and older patients following ACLR. Nevertheless, differences were observed in specific questionnaire domains across age categories. Postoperative knee instability was infrequent, occurring in 3.5% of all cases, and was more prevalent among male patients. This complication was observed predominantly in the youngest age group (under 25 years) and was not detected in patients aged 50 years or older.

Conclusion

In the present study, no detectable difference in overall quality of life was found between patients with isolated anterior cruciate ligament tears (Group A) and those with concomitant meniscal injuries (Group B). However, a clear and consistent disparity was observed in Lysholm score outcomes, with Group A demonstrating superior functional results both before and after reconstruction. These findings suggest that the presence of meniscal injury may adversely affect knee function in patients undergoing anterior cruciate ligament reconstruction. Future studies incorporating extending follow-up periods of 5, 10, or more years are warranted to provide a more comprehensive understanding of long-term impact of isolated versus combined anterior cruciate ligament and meniscal injuries on quality of life. Prolonged observation will also facilitate earlier detection of degenerative joint changes, including the development of osteoarthritis. Such long-term data are essential for determining whether combined injuries accelerate joint degeneration and for clarifying how progressive structural deterioration translates into functional impairment and patient-reported quality-of-life outcomes.

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REVIEW ARTICLES
PREGLEDNI ČLANCI

PREDICTION OF TOTAL KNEE ARTHROPLASTY OUTCOME BASED ON PSYCHO-PHYSICAL TESTS

PREDIKCIJA ISHODA TOTALNE ARTROPLASTIKE KOLENA NA OSNOVU PSIHOFIZIČKIH TESTOVA

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Abstract

Introduction. Osteoarthritis is the most prevalent joint disease worldwide, with knee osteoarthritis representing its most common form. Pain in knee osteoarthritis is known to have neuropathic components; however, the mechanisms leading to central sensitization remain incompletely understood. It is also unclear whether surgical pain relief achieved through total knee arthroplasty results in modulation of central sensitization and neuropathic pain. **Quantitative sensory testing in the prediction of postoperative pain after total knee arthroplasty.** Sensory profiling using quantitative sensory testing modalities – particularly temporal summation and conditioned pain modulation – has emerged as a valuable approach for identifying patients with osteoarthritis who are at risk of acute and chronic postsurgical pain. These modalities, when combined with other parameters, may facilitate individualized pain management strategies. Preoperative hyperalgesia and neuropathic pain features, detected through temporal summation testing and PainDETECT questionnaires, have demonstrated predictive value for the development of chronic postsurgical pain after total knee arthroplasty. Patients exhibiting centrally mediated pain mechanisms and established central sensitization tend to experience less postoperative pain relief following total knee arthroplasty. Female sex has been associated with higher magnitude of conditioned pain modulation and an increased prevalence of severe acute and chronic postsurgical pain, identifying it as a potential risk factor for pain chronification. **Conclusion.** Quantitative sensory testing modalities – particularly temporal summation, conditioned pain modulation, and pressure pain threshold – appear to be the most promising tools for predicting postoperative pain outcomes using quantitative sensory testing. Patients with evidence of central sensitization show reduced pain relief after total knee arthroplasty.

Key words: Osteoarthritis; Prognosis; Arthroplasty, Replacement, Knee; Treatment Outcome; Pain Measurement; Central Nervous System Sensitization; Pain, Postoperative

Sažetak

Uvod. Osteoartritis predstavlja najčešću bolest zglobova, pri čemu je osteoartritis kolena najzastupljeniji. Iako je poznato da bol kod osteoartritisa kolena delom jeste neuropatski bol, nejasno je koji mehanizam dovodi do centralne senzitizacije i da li će eliminacija bola hirurškom procedurom kao što je totalna artroplastika kolena dovesti do promena u vezi sa centralnom senzitizacijom i neuropatskim bolom. **Kvantitativno senzorno testiranje u predikciji postoperativnog bola nakon totalne artroplastike kolena**. Senzorno profilisanje pacijenata sa osteoartritisom korišćenjem kvantitativnog senzornog testiranja postalo je uobičajeno. Kvantitativni senzorni modaliteti, kao što su temporalna sumacija i uslovna modulacija bola, pokazali su se kao potencijalni prediktori akutnog i hroničnog posthirurškog bola i trebalo bi ih kombinovati sa drugim parametrima kako bi se postigla personalizovana terapija bola. Preoperativna hiperalgezija i neuropatski bol otkriveni tokom ispitivanja temporalne sumacije i pomoću upitnika *PainDETECT* imaju prediktivnu vrednost za razvoj hroničnog posthirurškog bola nakon totalne artroplastike kolena. Pacijenti sa centralno iniciranom senzitizacijom imaju nedovoljno smanjenje intenziteta bola nakon totalne artroplastike kolena. Ženski pol je povezan sa većim vrednostima uslovne modulacije bola i jačim akutnim i hroničnim posthirurškim bolom, izdvajajući se na taj način kao faktor rizika za hronifikaciju bola. **Zaključak.** Čini se da su modaliteti kvantitativnog senzornog testiranja kao što su temporalna sumacija bola, uslovna modulacija bola i prag bola na pritisak najperspektivniji modaliteti za pouzdano predviđanje postoperativnog bola uz pomoć kvantitativnog senzornog testiranja. Pacijenti kod kojih se detektuje prisustvo centralne senzitizacije imaju slabiju redukciju intenziteta bola nakon totalne artroplastike kolena.

Ključne reči: osteoartritis; prognoza; totalna artroplastika kolena; ishod lečenja; merenje bola; senzitizacija centralnog nervnog sistema; postoperativni bol

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Abbreviations

OA – osteoarthritis
KOA – knee osteoarthritis
CS – central sensitization
CNS – central nervous system
NP – neuropathic pain
CSI – Central Sensitization Inventory
QST – quantitative sensory testing
PDQ – Pain Disability Questionnaire
CPSP – chronic postsurgical pain
TKA – total knee arthroplasty
THA – total hip arthroplasty
TS – temporal summation
CPM – Conditioned Pain Modulation
PPT – pressure pain threshold
WUR – "wind up ratio"
APSP – acute postsurgical pain

Introduction

Osteoarthritis (OA) is a degenerative joint disease that develops primarily as a result of progressive loss of articular cartilage. It is the most common joint disorder worldwide, with the knee being the most frequently affected joint. OA predominantly affects older individuals and occurs more often in women. According to its etiology, osteoarthritis is classified as primary osteoarthritis, which has no identifiable cause, and secondary osteoarthritis, which arises due to a known underlying factor such as previous trauma or surgery, congenital limb malformations, or other conditions. [1,2]. The clinical presentation of osteoarthritis of the knee (KOA) is characterized by the gradual onset of symptoms including pain during walking and at the initiation of movement after periods of rest (e.g., prolonged lying or sitting), accompanied by reduced range of motion in the affected joint [3]. Initial management is based on non-surgical approaches, including patient education, physical therapy, and pharmacological therapy [4]. These conservative measures do not halt the degenerative process itself but can substantially reduce pain and functional disability. When conservative treatment no longer provides adequate symptom relief, surgical intervention may be indicated [5].

As with many chronic pain conditions, pain mechanisms in patients with KOA are multifactorial, complex and not yet fully understood [6]. Numerous studies have demonstrated a poor correlation between radiographic severity and the intensity of pain or degree of disability in OA [7,8], highlighting the contribution of biopsychosocial mechanisms to pain perception in KOA [9].

Pain duration has been shown to correlate with perceived pain intensity [10]. Present nociceptive input from peripheral tissues, together with altered modulation by the central nervous system, can initiate central sensitization (CS) [11]. Central sensitization is defined as an amplification of neural signaling from the periphery in the central nervous system (CNS), resulting in hypersensitivity [12,13]. The presence of CS may contribute to the development of a neuropathic pain (NP) component [14]. Although knee pain in KOA has been shown to include neuropathic pain (NP) [15,16], the precise mechanisms leading to CS remain unclear. Furthermore, it is not fully understood whether elimination of pain through surgical intervention, such as total knee replacement, results in reversal or modulation of CS and NP [17].

The Central Sensitization Inventory (CSI) and various quantitative sensory testing (QST) methods have been developed to assess clinical markers of CS [18,19]. SSensory profiling using quantitative sensory testing (QST), aimed at measuring and quantifying sensitization-related processes, has become increasingly common in clinical practice for patients with osteoarthritis. Recent studies have demonstrated that a substantial proportion of patients with KOA exhibit widespread hyperalgesia, enhanced temporal summation of pain, and impaired endogenous pain inhibition compared with healthy individuals. These alternations may influence pain transmission pathways and contribute to unfavorable long-term pain outcomes following arthroplasty [20].

Assessment of pain-related functional impairment is also essential for treatment planning and enhancing patients' quality of life [21]. Various instruments are available for this purpose, among which the Pain Disability Questionnaire (PDQ) has been shown to be a reliable and valid tool [22].

When conservative treatment fails to adequately reduce pain and improve function in patients with KOA, quality of life may be significantly compromised, and Total Knee Arthroplasty (TKA) may be indicated [23].

However, arthroplasty is associated with a considerable prevalence of chronic postsurgical pain (CPSP) [24], making identification of risk factors for its development clinically important. Several predictors have been proposed, including sociodemographic factors, pain mechanisms, psychological variables, and the presence of pain sensitization, yet the exact mechanisms underlying chronic pain remain incompletely understood [25]. Acute postoperative pain has also been recognized as a key predictor of CPSP and therefore represents a potential target for preventive strategies [26]. Current evidence supports the role of CS as a significant risk factor for persistent pain and patient dissatisfaction following TKA [12]. Although advances in pain management and surgical techniques have improved early postoperative recovery [27], the prevalence of CPSP remains high despite adequate early postoperative analgesia [28]. After TKA, reported rates of chronic pain range from 10%

to 34% and have remained largely unchanged for decades, often without a surgically identifiable cause [17].

The aim of the review was to analyze the available literature in order to determine the relevance of QST in predicting outcomes after TKA and to identify the most promising QST modalities for this purpose.

Quantitative Sensory Testing in the prediction of postoperative pain after total knee arthroplasty

QST modalities for reliable prediction of postoperative pain after TKA

According to current evidence, QST modalities such as temporal summation (TS) and conditioned pain modulation (CPM) appear to be the most promising tools for predicting postoperative pain [29]. Among various surgical populations, QST has demonstrated the strongest predictive value in patients undergoing orthopedic procedures [30]. In 2021, Brown et al. conducted a comprehensive literature review to assess the role of perioperative QST in predicting acute and chronic postoperative pain across different surgical disciplines. The authors analyzed studies employing a wide range of QST modalities to assess sensory perception, pain thresholds, and pain tolerance using standardized stimuli. These stimuli included pressure, vibration, thermal, and electrical inputs, which are commonly used to evaluate specific nerve fiber function, detect neuropathic pain, and identify neurological dysfunction. QST assessments typically measure sensory responses at the level of stimulus detection, pain threshold, and, when applicable, pain tolerance. Frequent used QST thermal tests include warm and cold detection thresholds, heat and cold pain thresholds, and pain intensity elicited by suprathreshold thermal stimuli. Mechanical testing is typically conducted with von Frey filaments, and pain thresholds are measured using blunt needles or pressure cuffs. Allodynia is assessed using soft materials such as cotton pads or brushes, while vibration perception is evaluated with tuning forks. Electrical QST modalities include electrical detection threshold, electrical pain threshold, and electrical pain tolerance. Pain intensity is typically quantified using the Numeric Pain Scale and the Visual Analogue Scale. The studies included in the review primarily focused on preoperative QST assessment across multiple surgical specialties. Although orthopedic surgery showed the strongest correlation between preoperative QST findings and postoperative pain outcomes, no single QST modality was identified as universally superior across all studies. Nevertheless, TS and CPM emerged as potential predictors of both acute and chronic postsurgical pain. Brown et al. concluded that the QST method should be combined with other parameters, such as preoperative pain intensity, anxiety, and pain catastrophizing, to enable personalized pain management [29].

QST and PainDETECT questionnaire in the prediction of postoperative pain after TKA

A recent study by Vygotsky et al. (2024) evaluated the predictive value of the QST and the PainDETECT questionnaire for postoperative pain at 3, 6, and 12 months following total knee arthroplasty. The study included 77 patients with KOA and 41 healthy controls. QST assessments were performed preoperatively and repeated at 3 and 6 months postoperatively, followed by the PainDETECT questionnaire. The QST protocol comprised pressure pain threshold (PPT), pain tolerance threshold, conditioned pain modulation (CPM) and temporal summation (TS). Preoperatively, patients with OA exhibited pinprick hyperalgesia on the medial aspect of the affected knee and increased sensitivity to cuff pressure on the ipsilateral lower leg compared with healthy controls. Preoperative pinprick hyperalgesia and the presence of pain with a neuropathic component were significant predictors of both preoperative pain intensity and pain intensity one year after surgery. Additionally, lower cuff pressure pain thresholds and mechanical hyperalgesia induced by needle stimulation were associated with higher preoperative pain intensity in patients with KOA. Baseline hyperalgesia assessed by TS accounted for 25% of the variance in pain intensity at 12 months postoperatively, while preoperative NP scores explained 30% and 20% of the variance in postoperative pain at 6 and 12 months, respectively. Importantly, a reduction in hyperalgesia at 3 months after surgery compared with baseline was associated with lower pain intensity at 12 months following TKA. These findings suggest that preoperative hyperalgesia and NP, identified through TS and the PainDETECT questionnaire, have significant predictive value for the development of CPSP after TKA [31].

QST and central sensitization inventory in the prediction of postoperative pain after TKA

Another study published in 2024 investigated whether pain intensity over time differs among patients with KOA undergoing TKA based on distinct somatosensory profiles. The study included 223 patients (mean age 66 years) and evaluated the evolution of QST measures and the CSI preoperatively and one year after TKA. Participants were categorized into three groups according to changes of somatosensory functioning across seven variables: local PPT, widespread PPT, local heat allodynia, widespread heat allodynia, TS, CPM, and CSI. The normal group dem-

onstrated normal somatosensory function both before and after TKA. The recovered group exhibited impaired somatosensory function preoperatively but normalized findings postoperatively. The persistently impaired group showed abnormal somatosensory functioning both pre- and postoperatively. Comparisons of pain intensity preoperatively, postoperatively, and one year after TKA revealed significant group differences in four of seven variables: local PPT, local heat allodynia, TS, and CSI. Patients with persistently impaired somatosensory function experienced less improvement in pain (based on CSI and local heat allodynia) and higher pain scores one year after TKA (based on CSI, local PPT and heat allodynia, and TS) compared with patients who maintained normal somatosensory functioning. Moreover, this group also demonstrated worse pain scores at one year compared with the recovered group (based on CSI). These findings indicate that patients exhibiting centrally mediated sensitization in four out of seven examined variables are less likely to achieve meaningful pain relief and exhibit poorer pain scores following TKA [32].

QST and gender in the prediction of postoperative pain after TKA

When sociodemographic predictors are considered, female sex is frequently associated with a greater magnitude of the CPM [33] and with more severe APSP and CPSP [34], although conflicting findings have also been reported. Several studies based on somatosensory profiling indicate that women tend to exhibit greater pain sensitivity and enhanced endogenous pain facilitation [35]. Despite evidence suggesting that women generally report higher levels of anxiety [36,37], some studies have demonstrated that the association between anxiety and pain intensity is stronger in men [38]. These findings raise the question of whether the phase of the menstrual cycle should be considered when interpreting QST results. However, some investigations report no significant differences in selected QST parameters and emotional states across different menstrual cycle phases [39].

Only a limited number of studies have directly examined the role of gender in the relationship between QST parameters and postsurgical pain. In a study by Bossmann et al., impaired endogenous pain inhibition assessed by CPM was associated with more severe postsurgical pain in women, but not in men [40]. These findings highlight the need for a more detailed evaluation of gender-specific mechanisms underlying the relationship between QST outcomes and postoperative pain after TKA.

One of the few studies explicitly addressing gender as a modifying factor in arthroplasty outcomes was conducted by Paredes et al. (2024). The authors investigated psychological and psychophysical variables associated with acute and chronic pain following TKA and total hip arthroplasty, and examined whether these relationships differed by sex. Assessments were performed 48 hours preoperatively and three months postoperatively, and included sociodemographic, pain-related, and psychological questionnaires, as well as QST. The study included 63 subjects (31 women, 32 men), of whom 34 (54%) underwent TKA and 29 (46%) underwent total hip arthroplasty (THA). Notably, most women underwent TKA, whereas most men underwent THA. Significant sex-related differences in QST parameters were observed at the hand, including mechanical stimulus detection thresholds, "wind up ratio" (WUR), and CPM. Women demonstrated lower mechanical sensitivity (higher mechanical stimulus detection threshold), greater pain facilitation (higher WUR) at both the hand and the affected joint, and reduced pain inhibition (higher CPM values) at the affected joint. No significant sex-based differences were observed in the analyzed variables 48 hours after surgery. However, at three months postoperatively, women reported significantly higher pain intensity than men. Acute postsurgical pain (APSP) at 48 hours was associated with impaired CPM, while CPSP at three months was associated with female sex, longer duration of preoperative pain, TKA, higher APSP intensity, and impaired CPM. In multivariate analysis, these clinical variables remained significant predictors of CPSP, with the exception of sex and CPM. Importantly, WUR was a significant predictor of APSP in men, whereas CPM was a significant predictor of CPSP in women. CPM of the affected joint emerged as the only QST measure demonstrating significant results at both time points: CPM assessed at the hand was related to acute pain, while CPM assessed at the affected joint was related to chronic pain. At both assessments, higher pain intensity was observed in patients with less efficient pain inhibition (higher CPM score). Patients with effective CPM at the hand experienced less pain at 48 hours, whereas those with effective CPM at the affected joint reported less pain at three months postoperatively. None of the psychological variables examined were significantly associated with pain intensity at either postoperative time point. In this trial, women reported higher pain intensity preoperatively and at three months postoperatively, supporting previous evidence that female sex is a risk factor for pain chronification [41]. It is important to note that most women in this study underwent TKA, whereas most men underwent THA. Since THA is associated with lower incidence of CPSP than TKA [42], and TKA is known to be associated with greater postoperative pain

and lower improvement rates [43], the observed sex-related differences in CPSP may be partially attributable to procedure-specific factors. Furthermore, women tend to undergo surgery at more advanced stages of osteoarthritis, often with a longer duration of preoperative pain, which may contribute to greater pain severity both before and after surgery [41].

Conclusion

Given the increasing prevalence of knee osteoarthritis, it is essential to identify reliable methods for predicting outcomes following operative treatment, particularly total knee arthroplasty, in order to optimize postoperative pain management. Quantitative sensory testing modalities – especially pressure pain threshold, temporal summation, and conditioned pain modulation – have emerged as the most promising tools within quantitative sensory testing for predicting postoperative pain outcomes.

Evidence indicates that specific quantitative sensory testing parameters are associated with an increased risk of acute and chronic postsurgical pain, and that the associations may differ according to gender. This underscores the importance of recognizing that risk factors for pain chronification are not uniformly applicable to all patients, and that predictive models must be tailored to specific patient subgroups. The moderating role of gender may help explain the conflicting findings reported in the quantitative sensory testing literature. Future research should take into account the type of surgical procedure (total knee arthroplasty versus total hip arthroplasty) when assessing postoperative pain outcomes.

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CASE REPORTS
PRIKAZI SLUČAJEVA

TESTICULAR TORSION AS A RARE UROLOGICAL COMPLICATION FOLLOWING INGUINAL HERNIA REPAIR

TORZIJA TESTISA KAO RETKA POSTOPERATIVNA KOMPLIKACIJA NAKON INGVINALNE HERNIOPLASTIKE

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Case report
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Abstract

Introduction. Surgical repair of inguinal hernias is among the most commonly performed procedures in general surgery. Despite the high volume of operations performed annually, urological complications following this procedure remain underreported. Testicular torsion is one of the most frequent causes of an acute scrotum; however, it is rarely considered a postoperative complication, which may delay diagnosis and subsequently increase the risk of testicular loss. **Case Report.** We present the case of a 47-year-old male who was admitted to the Emergency Department with scrotal pain occurring three days after an elective right-sided inguinal hernia repair. Physical examination and scrotal color Doppler ultrasonography were performed, after which urgent surgical exploration was indicated. Intraoperatively, a 360º intravaginal torsion of the right spermatic cord was identified, with no restoration of blood flow following detorsion. Based on intraoperative findings, a right-sided orchiectomy was performed. The diagnosis was subsequently confirmed by histopathological examination. **Conclusion.** Although postoperative symptoms may be nonspecific and misleading, clinicians should maintain a high level of suspicion for possible urological complications after inguinal hernia repairs. Delayed recognition can significantly impact a patient's quality of life and may result in considerable medico-legal consequences. Early identification and prompt management are thereof essential.

Key words: Spermatic Cord Torsion; Hernia, Inguinal; Herniorrhapy; Postoperative Complications; Orchiectomy

Sažetak

Uvod. Hirurške reparacije ingvinalne hernije imaju veliku učestalost u svakodnevnoj kliničkoj praksi. Uzimajući u obzir broj izvedenih operacija, urološke komplikacije koje prate ovu proceduru veoma se retko sreću u dostupnoj literaturi. Torzija testisa jedna je od najčešćih kliničkih prezentacija akutnog skrotuma koja se retko razmatra kao moguća postoperativna komplikacija. Reparacija ingvinalne hernije praćena testikularnom torzijom je slučaj koji se retko sreće u svakodnevnoj praksi što može dovesti do izostanka pravovremenog tretmana i gubitka testisa. **Prikaz bolesnika.** Predstavljamo 47-godišnjeg pacijenta koji se javio u Urgentni centar zbog bola u desnom hemiskrotumu tri dana nakon elektivne hirurške reparacije desnostrane ingvinalne hernije. Nakon fizikalnog pregleda i ultrazvučnog pregleda skrotuma indikovana je urgentna hirurška eksploracija. Na osnovu intraoperativno uočene intravaginalne torzije desne spermatične vrpce za 360 stepeni, bez očuvane cirkulacije nakon detorzije, indikovana je desnostrana orhiektomija. Patohistološki nalaz potvrdio je kliničku dijagnozu. **Zaključak.** Iako retko razmatrane, urološka stanja kao postoperativne komplikacije mogu imati izuzetno negativan efekat na kvalitet života pojedinca zbog čega je neophodna pravovremena dijagnostika i adekvatan tretman.

Ključne reči: torzija testisa; ingvinalna hernija; herniorafija; postoperativne komplikacije; orhiektomija

Introduction

Testicular torsion (TT) represents a twisting of the spermatic cord and its structures, leading to venous congestion, reduced testicular perfusion, and subsequent ischemia. This results in oxidative stress and irreversible damage to testicular tissue. It is one of the most important clinical presentations within the spectrum of acute scrotum. Patients typically present with sudden unilateral scrotal pain, often accompanied by nausea and vomiting. Testicular torsion can occur at any age; however it is most prevalent in the neonatal period and among adolescents aged 12 to 18 years. The overall incidence is estimated at 1 in 4,000 males under

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Abbreviations
TT – testicular torsion
IH – inguinal hernioplasty

25 years of age, while another study reported an annual incidence of 3.8 per 100,000 males younger than 18 years. Although commonly considered a condition of young patients, up to 14% of cases occur in adults [1].

Although rarely discussed, TT may occur as a postoperative complication following inguinal hernioplasty (IH). Prompt diagnosis in the early postoperative period is challenging, as several conditions can mimic its clinical presentation [2]. The most frequently reported urological complication following IH is ischemic orchitis, whereas TT remains exceedingly rare in the available literature. The treatment of choice in all suspected cases of TT is urgent surgical scrotal exploration to restore testicular perfusion.

Case report

A 47-year-old male presented to the Emergency Department with sudden onset of right-sided scrotal pain, accompanied by swelling of the right testicle and fever up to 38.5 °C. Two days prior, ha had undergone an elective right-sided inguinal hernioplasty (IH). Laboratory findings showed leukocytosis of 19.61 × 10^9/L (reference: 4–10 × 10^9/L) and markedly elevated C-reactive protein of 280.1 mg/L (reference: 0–5 mg/L). Remaining laboratory parameters were within normal limits. Physical examination revealed a swollen, edematous scrotum with a high-riding right testicle and an absent cremasteric reflex. Scrotal color Doppler ultrasonography demonstrated a heterogeneous right testicle with no detectable blood flow. Based on these findings, immediate surgical exploration was indicated. During the operation, after opening the parietal layer of the tunica vaginalis, a hematocele was observed. Further inspection revealed a 360º intravaginal torsion of the spermatic cord and a dark purple, ischemic testis **(Figure 1).** The testis was detorsed and warmed in moist gauze; however, no signs of reperfusion were observed. The right testicle and epididymis remained nonviable. Given these intraoperative findings, a right-sided orchiectomy was performed. Tissue samples were sent for histopathological examination. Histopathology confirmed the clinical diagnosis, revealing massive testicular necrosis affecting all seminiferous tubules, likely as a consequence of compromised vascular supply following prior surgical manipulation.

Figure 1. Intraoperative findings of 360º torsion of the spermatic cord and ischemic dark purple testis

The postoperative course was uneventful, and the patient was discharged three days after surgery.

Discussion

Testicular torsion can be classified into an intravaginal and an extravaginal form. The intravaginal form most commonly occurs as a consequence of an abnormal attachment of the tunica vaginalis, which allows the spermatic cord to rotate within it. In contrast, in the extravaginal form the tunica vaginalis is not attached to the gubernaculum, causing the tunica vaginalis and spermatic cord to twist together. The pathophysiological mechanism in our case can be attributed to the extravaginal type, in which a 360º torsion of the spermatic cord and tunica vaginalis occurred due to intraoperative manipulation of the cord. This resulted in venous congestion and testicular edema, subsequently reducing arterial flow and causing ischemia [1].

Although inguinal hernia repair is among the most commonly performed surgical procedures, only a limited number of studies describe urological complications following IH. Overall postoperative complications after IH occur in 8-10% of cases, whereas urological complications remain underreported. Certain groups of patients, including those of advanced age, individuals with diabetes, smokers, patients undergoing emergency hernia repair, those operated under specific types of anesthesia, and individuals with bilateral hernias, are at increased risk of postoperative complications [3,4].

Postoperative urological complications can be categorized as intraoperative, immediate postoperative, and long-term complications.

Intraoperative complication described in case reports include bladder injury and damage to spermatic cord structures. Many of these complications can be recognized during surgery and managed promptly. The risk of intraoperative urogenital injury varies depending on the surgical technique and mesh material used [5].

Immediate postoperative complications include various forms of orchitis (bacterial or ischemic), urinary infections, hydrocele, and scrotal hematoma.

Although these conditions may appear alarming and cause significant patient discomfort, most resolve with conservative management.

Long-term complications represent a greater clinical concern. Chronic orchialgia and testicular atrophy may lead to infertility and substantially impair quality of live. Testicular pain that becomes chronic and remains untreated can result in irreversible ischemic damage. True underlying cause of post-hernia repair testicular pain is often uncertain and may be vascular, neurological, or originate from paratesticular structures. If cases where TT is suspected, immediate scrotal exploration is mandatory [6,7].

When the testicle is involved, prognostic factors such as the duration of symptoms, physical examination findings, imaging results, and laboratory data must be considered to differentiate complications requiring urgent surgical management. Non-specific symptoms such as nausea, vomiting, scrotal swelling, and tenderness, when associated with TT, are typically accompanied by specific signs on physical examination, including a high-riding testicle, scrotal skin retraction, and absence of the cremasteric reflex. These findings are incorporated into several clinical scoring systems developed to estimate the likelihood of TT [2]. While laboratory findings have limited diagnostic value, scrotal color Doppler ultrasonography remains the most reliable imaging modality for distinguishing TT from other causes of acute scrotum, owing to its high sensitivity and specificity [8,9]. If TT is suspected, urgent scrotal exploration is the treatment of choice. Testicular salvage rates depend heavily on the time elapsed from symptom onset [10]. The optimal timeframe for detorsion and revascularization is within six hours, when the salvage rate is approximately 90%. This rate decreases dramatically with time and may fall to as low as 10% when revascularization occurs within 12-24 hours [11,12].

Conclusion

Given the high prevalence of inguinal hernias and the large number of inguinal hernia repairs performed annually, the true incidence of urological complications is likely underestimated. These complications can significantly affect an individual's quality of life and may, in some cases, cause greater harm then the hernia itself. Symptoms may be misleading and can appear several days after surgery, increasing the risk of missing the optimal window for treatment. Moreover, the medico-legal implications of delayed or missed diagnoses represent an additional burden for healthcare institutions, particularly when patients present weeks or months after surgery, when testicular salvage rates are extremely low. Thorough identification of anatomical structures and careful patient selection are essential to reduce the risk of postoperative complications. Raising awareness of rare but serious complications such as postoperative testicular torsion is crucial to ensure timely diagnosis and immediate intervention.

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INHERITED EPIDERMOLYSIS BULLOSA – ASSOCIATED CUTANEOUS SQUAMOUS CELL CARCINOMA ON THE LEG – WHEN TO AMPUTATE?

HEREDITARNA EPIDERMOLIZA – SKVAMOZNI KARCINOM NA NOZI – KADA JE VREME ZA AMPUTACIJU?

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Abstract
Introduction. Inherited epidermolysis bullosa comprises a heterogeneous group of genetic disorders characterized by skin fragility, resulting in blisters, erosions, and scaring of the skin and mucous membranes following minimal mechanical trauma. Patients with inherited epidermolysis bullosa are at increased risk of developing aggressive cutaneous squamous cell carcinoma, most commonly arising on the extremities. **Case Report.** We report a case of a 21-year-old female with inherited epidermolysis bullosa who presented with a progressively enlarging tumor on the right lower leg, appearing as a small crusted lesion. Physical examination revealed a firm, elevated lesion measuring approximately 10 cm in greatest diameter, covered with crusts. The patient had previously undergone two surgical excisions the same site for confirmed cutaneous squamous cell carcinoma. Radiological evaluation demonstrated no evidence of bone invasion, while ultrasonography identified a single enlarged lymph node in the right inguinal region. Partial biopsy of the lesion confirmed cutaneous squamous cell carcinoma, and lymph node biopsy revealed reactive lymphadenitis without metastatic involvement. Considering the presence of typical lesions throughout the body, the patient's inability to achieve verticalization, limited reconstructive options, and repeated recurrence of aggressive carcinoma, limb amputation was considered the most appropriate therapeutic approach. **Conclusion.** In patients with inherited epidermolysis bullosa who develop recurrent cutaneous squamous cell carcinoma, particularly after multiple local recurrences and in the absence of feasible reconstructive options, amputation may represent an unavoidable yet life-preserving treatment strategy, even in the setting of localized disease.
Key words: Epidermolysis Bullosa; Carcinoma, Squamous Cell; Amputation, Surgical; Recurrence

Sažetak
Uvod. Hereditarna epidermoliza predstavlja grupu genetskih poremećaja povezanih sa povećanom osetljivošću kože, koja dovodi do formiranja plikova, erozija i ožiljaka na koži i sluzokoži i to kao odgovor na minimalnu mehaničku traumu. Hereditarna epidermoliza je povezana sa povećanim rizikom od agresivnog kutanog skvamoznog karcinoma, koji se javlja češće na ekstremitetima. **Prikaz slučaja.** Pacijentkinja stara 21 godinu, koja boluje od hereditarne epidermolize, javila se lekaru sa tumorom na desnoj nozi. Tumor je započeo u formi male kruste koja je postepeno počela da raste tokom vremena. Fizikalnim pregledom otkrivena je lezija lokalizovana na desnoj potkolenici, iznad nivoa kože, ovalnog oblika, 10 cm u najvećem prečniku, tvrde konzistencije, prekrivena krustama. Ranije je imala dve operacije sličnih lezija na istom mestu (Ph: kutani skvamozni karcinom). Radiološka dijagnostika nije pokazala infiltraciju kostiju, a ultrazvučno je viđen samo jedan uvećan limfni čvor u desnom ingvinumu. Parcijalna biopsija lezije potvrdila je skvamozni karcinom, a biopsija limfnog čvora reaktivni limfadenitis bez prisustva metastatskih ćelija. S obzirom na prisutnost tipičnih lezija po celom telu, nemogućnost vertikalizacije pacijentkinje, nedostatka resursa za rekonstrukciju, i prisutnog recidiva agresivnog kutanog skvamoznog karcinoma, amputacija se smatrala optimalnim rešenjem. **Zaključak.** Kod pacijenata koji boluju od hereditarne epidermolize, sa dve ili više recidiva kutanog svamoznog karcinoma i uz dodatni nedostatak lokalnih mogućnosti hirurške rekonstrukcije, bez obzira na to što se radi o lokalizovanoj bolesti, amputacija može biti nevoljno, ali neophodno rešenje.
Ključne reči: epidermoliza; skvamozni karcinom; amputacija; recidiv

Introduction

Inherited epidermolysis bullosa (IEB) represents a heterogeneous group of genetic disorders characterized by skin fragility, leading to blister formation, erosions, and wounds of the skin and mucous membranes following minor mechanical trauma. IEB encompasses a wide spectrum of phenotypes, ranging from severe cutaneous and extracutaneous involvement caused by deficiencies in key adhesion proteins to mild cutaneous fragility characterized by subtle molecular defects [1]. Epidemiological data regarding the incidence and prevalence of EB vary considerably across studies worldwide, and to date, epidemiological studies on IEB have been con-

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Abbreviations

IEB – inherited epidermolysis bullosa
EBS – epidermolysis bullosa simplex
JEB – junctional epidermolysis bullosa
DEB – dystrophic epidermolysis bullosa
KEB – Kindler epidermolysis bullosa
BMZ – basement membrane zone
cSCC – cutaneous squamous cell carcinoma
LN – lymph node

ducted in Serbia. Based on 16 years of data collection in the United States, the overall incidence and prevalence of IEB were estimated at 19.57 per 1 million live births and 11.07 per 1 million population, respectively [2].

Four major classical types of IEB are recognized: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler epidermolysis bullosa (KEB). The classification of IEB is complex, as mutations within the same gene may be inherited in either an autosomal dominant or recessive manner, resulting in distinct clinical phenotypes. Conversely, similar phenotypes observed in DEB and EBS may arise from mutations in different genes, which can also be inherited in either dominant or recessive forms [3]. The diagnosis of IEB is primarily based on clinical assessment, supported by skin biopsy with histopathological analysis and genetic testing to identify disease-specific mutations. Additional diagnostic tools, including immunofluorescence mapping and transmission electron microscopy, may further assist in subtype differentiation and disease characterization.

Damages occurring within or beneath the cutaneous basement membrane zone (BMZ) lead to chronic, fibrotic, and inflamed wounds that heal with scarring. Patients afflicted by IEB are therefore at a markedly increased risk of developing one or more cutaneous squamous cell carcinomas (cSCC), particularly at sites of long-standing, non-healing wounds and scarring. These tumors may result from genetic alterations that disrupt key regulatory pathways, leading to aberrant cell growth and malignant transformation within injured skin [4]. Potential pathogenic mechanisms include upregulation of basic fibroblast growth factor, mutations in the p53 gene, and reduced activity of natural killer cells [5]. In patients with recessive DEB, these cSCC are particularly aggressive and frequently represent the leading cause of mortality within [4].

In individuals with IEB, cSCC most commonly arises within chronic, non-healing ulcers located over bony prominences. Early detection of malignant transformation is often challenging, as cSCC may closely resemble typical chronic ulceration characterized by scarring and crusting. Similar to tumors arising in burn scars, EB-associated cSCC typically originate at the margins of chronic ulcers.

Although variations in age of onset, tumor localization, and carcinogenic mechanisms exist among different IEB subtypes, IEB-associated cSCC represent a valuable clinical model for studying the interconnected mechanisms driving carcinogenesis within a fibrotic and inflammatory environment.

Case Report

A 21-year-old patient with IEB presented with tumor on her right leg. The lesion initially appeared as a small crust and progressively enlarged over time. Physical examination revealed an oval lesion located on the right lower leg below the knee measuring approximately 10 cm in maximum diameter and elevated up to 1 cm above the skin surface. The lesion was firm in consistency, brown in color, and covered with scaly crusts. In addition to the suspicious tumor lesion, multiple areas of de-epithelialization were observed both in the perilesional region and diffusely over the patient's body. The patient had previously undergone two surgical excisions of similar lesions in the same site (Ph: cSCC). Following there earlier interventions, the case was reviewed by the Oncology Committee, which recommended close clinical follow-up with regular assessment of local and locoregional status, without adjuvant therapy, due to the patient's underlying condition. At the time of this third recurrence, radiological imaging showed no evidence of bone infiltration. Ultrasonographic examination revealed a single enlarged right inguinal lymph node (LN). Partial biopsy of the lesion confirmed cSCC, while biopsy of the lymph node did not show evidence of metastatic involvement. The case was discussed at a multidisciplinary team meeting involving a plastic surgeon, orthopedic surgeon, oncologist, and psychologist. Vacuum-assisted closure (VAC) therapy was considered; however, it was deemed contraindicated due to the extreme skin fragility associated with IEB, which carries a high risk of additional tissue damage. Taking into account the presence of typical lesions in patients with IEB throughout the body, the patient's inability to achieve verticalization, the lack of reconstructive surgical options, and the repeated recurrence of aggressive carcinoma, limb amputation was determined to be the most appropriate therapeutic option. A supracondylar amputation of the lower right leg was therefore indicated and performed **(Figure 1).** The postoperative course was uneventful, with satisfactory wound healing and no complications **(Figures 2 and 3).** Unfortunately, due to the underlying disease and preexisting joint contractures, which had prevented ver-

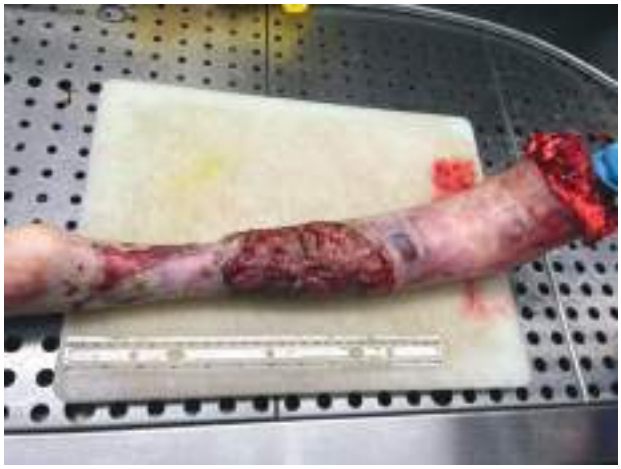
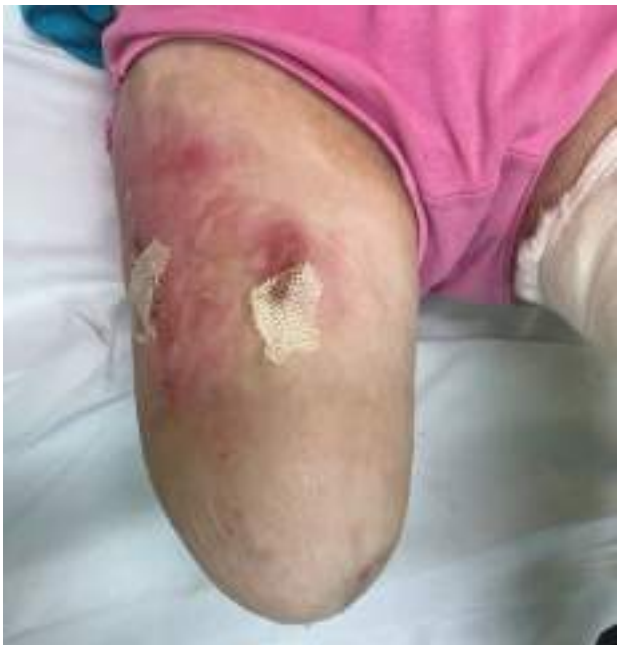
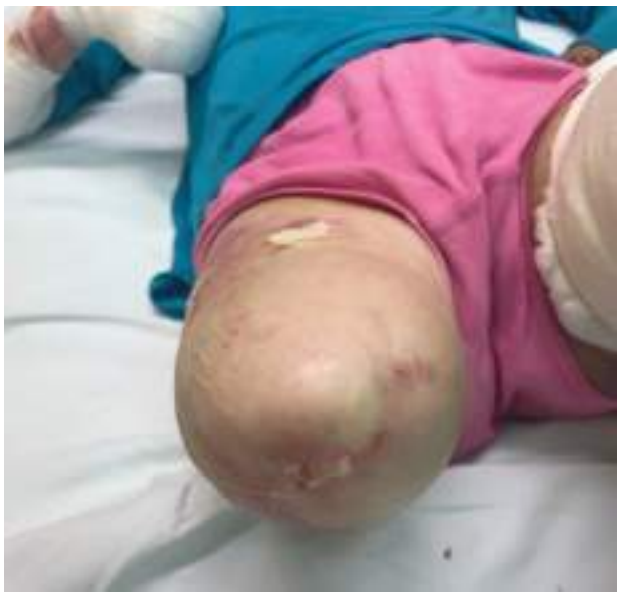


Figure 1. Supracondylar amputation of the lower right leg





Figures 2 and 3. Three months postoperatively

ticalization even prior to the amputation, prosthetic fitting of the lower limb was not feasible.

Discussion

Inherited epidermolysis bullosa (IEB) is a heterogeneous group of disorders characterized by a wide spectrum of clinical severity, diverse inheritance patterns, and numerous causative genetic mutations. The most severe forms are associated with profound morbidity, including chronic pain, recurrent infections and inflammation, limb amputations, and reduced life expectancy [6]. Individuals afflicted by IEB have a markedly increased risk of developing cSCC, particularly at sites of chronic, non-healing wounds and scarred skin.

Published data indicate that patients with IEB develop cSCC at a significantly younger age compared with the general population, with a mean age at diagnosis of approximately 36 years versus around 80 years in non-IEB individuals [7].

Prognostic factors such as poor differentiation, tumor diameter greater than 2 cm, perineural invasion, and invasion beyond the subcutaneous fat are inconsistently reported in the literature, complicating the staging process. In particular, perineural invasion and depth of invasion are rarely addressed in the literature.

The preferred treatment involves performing a wide and deep surgical excision. Mellerio et al. recommended a minimum surgical margin of 2 cm around the tumor based on clinical assessment [8]. However, accurate delineation of tumor margins is often challenging and surgical margins are frequently limited by surrounding structures. Even when clear margins are achieved, complete disease control is not guaranteed. Surgical treatment is often aggressive, especially in advanced tumors, and prolonged wound healing is common. Consequently, limb amputation is frequently required [8]. Montaudie et al. reported that amputation was necessary in approximately 25% of IEB patients diagnosed with cSCC [7]. In the present case, amputation was performed after the second recurrence. Neoadjuvant radiotherapy may theoretically reduce tumor size and minimize surgical intervention; however, its use in patients with IEB requires extreme caution. The fragile skin and impaired regenerative capacity characteristic of IEB - particularly in generalized forms - significantly increase the risk of radiation-induced toxicity, delayed wound healing, and ulcer formation. Similarly, systemic chemotherapy with cytotoxic agents such as cisplatin combined with 5-fluorouracil or doxorubicin has shown some efficacy in advanced cSCC, but its substantial toxicity limits its use in patients with IEB and is generally not recommended [9].

In selected cases, a surgically aggressive approach, including amputation, may be necessary to minimize the risk of future recurrences. A crucial question remains: after how many tumor recurrences should amputation be considered the preferred therapeutic option? The answer is highly individualized and depends on multiple factors, including tumor stage and patient functional status. Early detection of regional lymph node metastases may improve prognosis. However, in IEB patients, lymph node enlargement is frequently caused by chronic inflammation or infection, increasing the risk of false-positive findings during staging. Systemic therapies, including conventional chemotherapy and newer targeted therapies may be considered in palliative settings, with careful evaluation of potential adverse effects. Psychological support is essential for patients with IEB and their families [10]. Additionally, mirror therapy may provide benefits for amputated patients by improving motor function, manual dexterity, fine motor skills, and range of motion when practiced consistently over time [11].

Conclusion

In patients with inherited epidermolysis bullosa who develop recurrent cutaneous squamous cell carcinoma and face limitations related to verticalization and local reconstructive surgery, limb amputation may represent a necessary last–resort treatment. This approach is aimed to reduce the risk of further disease progression and serious complications. The complexity of inherited epidermolysis bullosa-associated cutaneous squamous cell carcinomas underscores the need for multidisciplinary approach and the ongoing need of improved therapeutic options.

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CONSERVATIVE MANAGEMENT OF GALLBLADDER PERFORATION – CASE REPORT AND LITERATURE REVIEW

KONZERVATIVNO LEČENJE PERFORACIJE ŽUČNE KESE – PRIKAZ SLUČAJA I PREGLED LITERATURE

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Case report
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Abstract
Introduction. Gallbladder perforation is a rare but potentially life-threatening complication of acute cholecystitis, with reported mortality rates exceeding 50%. Owing to its frequently non-specific symptoms, early diagnosis is essential. Radiological imaging – particularly contrast-enhanced computed tomography and ultrasonography – plays a key role in identifying perforation. **Case Report.** We present the case of a 62-year-old patient with Niemeier Type II gallbladder perforation. At admission, prominent clinical or laboratory indicators of acute disease were absent. Initial management included broad-spectrum antibiotics and supportive therapy. Although percutaneous drainage was considered, the procedure was deemed unfeasible due to the close proximity of the abscess to the hepatic flexure of the colon. Consequently, an open cholecystectomy with abscessotomy was performed two weeks after symptom onset. The postoperative course was uneventful, and the patient was discharged on the fifth postoperative day for continued outpatient care. **Conclusion.** While surgical intervention is mandatory in cases of generalized biliary peritonitis, the optimal treatment strategy for localized gallbladder perforations remains debated. Current literature emphasizes the advantages of open cholecystectomy despite longer hospitalization, whereas delayed surgical intervention may be beneficial in carefully selected patients.
Key words: Gallbladder Diseases; Conservative Treatment; Cholecystitis, Acute; Drainage; Cholecystectomy

Sažetak
Uvod. Perforacija žučne kese predstavlja retku, ali ozbiljnu komplikaciju akutnog holecistitisa, sa mortalitetom preko 50%. Rano postavljanje dijagnoze je ključno, s obzirom na često nespecifične simptome. Radiološka dijagnostika, naročito kontrastno pojačana kompjuterizovana tomografija i ultrazvuk, igraju ključnu ulogu u identifikaciji perforacije. **Prikaz slučaja.** U ovom radu prikazujemo slučaj 62-godišnjeg pacijenta sa *Niemeier tip II* perforacijom žučne kese, bez izraženih kliničkih i laboratorijskih znakova akutne bolesti. Po prijemu, primenjena je inicijalna terapija antibioticima i potporne mere. Iako je perkutana drenaža razmatrana, nije mogla biti sprovedena zbog blizine hepatične fleksure kolona. Zbog toga je, dve nedelje nakon početka simptoma, sprovedena otvorena holecistektomija sa apscesotomijom. Postoperativni tok protekao je bez komplikacija, te je pacijent otpušten na dalje ambulantno lečenje petog postoperativnog dana. **Zaključak.** Iako je hirurška intervencija standard za generalizovani bilijarni peritonitis, optimalni pristup za lokalizovane perforacije ostaje predmet rasprava. Savremena literatura ukazuje na prednost otvorene holecistektomije, uprkos dužem boravku u bolnici, dok bi odložena operacija mogla biti korisna kod odabranih pacijenata.
Ključne reči: bolesti zučne kese; konzervativno lečenje; akutni holecistitis; drenaža; holecistektomija

Introduction

Gallbladder perforation is a rare but potentially life-threatening complication of acute cholecystitis, with mortality rates reported as high as 50% [1,2]. According to Niemeier's classification, perforations are categorized into three types: Type I (acute free perforation into the peritoneal cavity), Type II (subacute perforation with localized abscess formation), and Type III (chronic perforation with cholecystoenteric fistula) **(Table 1).** Spontaneous perforation occurs in approximately 2–10% of patients with acute cholecystitis and often presents with nonspecific symptoms, which complicates timely diagnosis. Clin-

Table 1. Niemeier classification of gallbladder perforation

Niemeier classification	
Type I	acute free perforation
Type II	subacute perforation with abscess formation
Type III	chronic perforation with cholecystoenteric fistula

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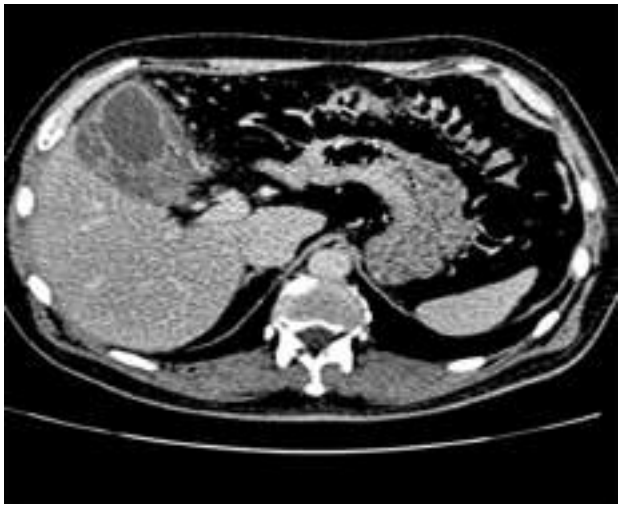

Figure 1. Contrast-enhanced abdominal CT scan showing a localized pericholecystic abscess

ical deterioration accompanied by fever, localized abdominal pain, and signs of sepsis should raise suspicion of perforation. The fundus of the gallbladder is most commonly affected site due to its relatively poor vascular supply. Comorbidities such as diabetes mellitus, hypertension, and immunosuppression significantly increase the risk of gallbladder perforation [6,7]. Contrast-enhanced computed tomography (CT) **(Figure 1)** is considered the gold standard for early detection, particularly in patients with atypical clinical presentations. While generalized biliary peritonitis (Type I) requires urgent surgical intervention, the optimal therapeutic approach for localized perforations (Type II) remains a matter of ongoing discussion. Over the past decade, increasing evidence has highlighted the potential role of conservative management in carefully selected patients, particularly when clinical stability is preserved and anatomical or systemic factors render surgery high-risk [9–13]. Conservative treatment typically includes broad-spectrum antibiotics, intravenous fluid therapy, ulcer and anticoagulation prophylaxis, and continuous clinical monitoring. When percutaneous drainage of the abscess is technically unfeasible or contraindicated, such non-operative management may provide a safe alternative to immediate surgery. In chronic perforations with fistula formation (Type III), conservative therapy may also serve as a temporary measure until elective surgical correction is feasible.

A growing body of case reports and review articles supports this strategy, demonstrating lower complication rates and shorter recovery periods in selected patients managed non-operatively compared to those undergoing emergency cholecystectomy [9–11]. Consequently, conservative management of gallbladder perforation has emerged as a valuable option in contemporary clinical practice, requiring careful assessment of patient-specific risk factors, overall clinical status, and the availability of interventional resour**ces.**

Case Report

A 62-year-old male patient was hospitalized without evident signs of acute illness. Two weeks prior to admission, he had experienced epigastric pain and nausea, which resolved spontaneously. On presentation, laboratory findings did not indicate acute inflammation, while abdominal ultrasonography revealed gallbladder wall thickening and pericholecystic fluid.

Radiological evaluation consisted of ultrasonography and contrast-enhanced CT of the abdomen, which demonstrated gallbladder distension, wall thickening, inflammatory changes, and a pericholecystic abscess measuring 17×14×10 mm located within liver segment S4b **(Figure 1).** Further imaging assessment showed that the abscess was in close proximity to the hepatic flexure of the colon, complicating the possibility of a safe percutaneous drainage approach.

Interventional radiology was consulted; however, percutaneous abscess drainage was deemed contraindicated due to the high-risk anatomical location and the significant risk of injuring the adjacent colon.

Therapeutic Approach

In the absence of clinical signs consistent with an acute abdomen, the patient was initially managed conservatively. The therapeutic regimen included: **broad-spectrum intravenous antibiotics** to cover potential polymicrobial infection, intravenous **crystalloid therapy** to ensure adequate hydration and hemodynamic stability, **prophylactic anti-ulcer treatment** to prevent stress-related gastrointestinal complications, **anticoagulation therapy** to reduce the risk of thromboembolic events.

Because no safe non-operative drainage option was available and abscess control was required, surgical treatment was planned. The patient underwent a surgery two weeks after symptom onset and ten days after admission. Intraoperatively, a chronically inflamed gallbladder containing a gallstone and a small subhepatic abscess collection were observed. Open cholecystectomy with abscess drainage was performed.

The postoperative course was uneventful. At follow-up seven days after discharge, the patient was asymptomatic, pain-free, and laboratory and clinical parameters remained within reference ranges. At the time of manuscript preparation – one year after hospitalization – the patient remained clinically stable, without signs of medical or surgical complications. The case illus-

trates that in selected patients with gallbladder perforation who present without acute abdominal signs, initial conservative management with close clinical monitoring may be appropriate. Nevertheless, surgical intervention becomes necessary when anatomical constraints preclude minimally invasive procedures.

Discussion

In the study by Petaković et al., *Acute cholecystitis – early or delayed cholecystectomy*, the authors confirmed the advantages of early cholecystectomy in the management of acute cholecystitis. Whether these benefits can be extrapolated to cases of gallbladder perforation, however, remains an open question [16].

Gallbladder perforation occurs in approximately 2–10% of patients with acute cholecystitis. While Type I perforations necessitate urgent surgical intervention, optimal treatment strategies for Type II and III perforations continue to be debated.

An expanding body of evidence supports the role of conservative management in selected cases of gallbladder perforation, particularly in patients presenting with localized disease and preserved clinical stability. In a retrospective study from 2006, Derici et al. [5] analyzed 13 cases of gallbladder perforation and reported favorable outcomes with non-operative treatment in patients with Type II perforation (localized abscess), provided that signs of diffuse peritonitis were absent. Similarly, Date et al. (2012) [15], in a prospective study involving 50 patients, demonstrated that early diagnosis combined with individualized therapeutic strategies – including conservative management in clinically stable patients – can significantly reduce morbidity. Although older, the study by Roslyn et al. (1987) [2] provides important insight into the natural history of cholecystitis and gallbladder perforation, showing that patients with mild symptoms and no systemic signs of infection may be safely managed with close monitoring and supportive care.

These studies collectively reinforce the concept that conservative treatment may serve as a viable and safe alternative to immediate surgical intervention in carefully selected individuals, particularly when invasive procedures carry elevated risk.

Recent literature highlights the relevance of conservative strategies. In Type II perforations, antibiotic therapy combined with vigilant clinical monitoring has proven effective, especially when anatomical constraints preclude percutaneous drainage (An Overview of the Management of Gallbladder Perforations, GJSCR) [12]. In Type III perforations with fistula formation, successful conservative management until elective surgical has been reported, demonstrating the safety of this approach in stable patients. Moreover, recent studies indicate that non-operative management may achieve short-term outcomes comparable to laparoscopic surgery in selected cases (Effectiveness of Conservative Management Versus Laparoscopic Surgery, BMJ, 2023) [13,14].

A systematic review by Quiroga-Garza et al. [8], including 122 patients with Type II perforation, concluded that although open cholecystectomy is associated with a lower likelihood of requiring additional procedures, it is also linked to longer hospitalization. Consistent with this, Krecko et al. [9], analyzing 654 patients, found that open cholecystectomy resulted in prolonged postoperative recovery and higher complication rates.

Further support for conservative treatment comes from clinical experience describing successful non-operative management in patients lacking signs of diffuse peritonitis. Intravenous antibiotic therapy, fluid resuscitation, and close clinical monitoring were sufficient to ensure clinical improvement without the need for surgical intervention. This emphasizes the potential safety of conservative therapy in well-selected, clinically stable patients, particularly when invasive procedures pose increased risk.

According to the Tokyo Guidelines for the management of acute cholecystitis [10], therapeutic decisions should be tailored to disease severity. While laparoscopic cholecystectomy remains the preferred treatment when feasible, conservative therapy is an acceptable option in high-risk patients or when surgery is contraindicated.

Conclusion

Early diagnosis and appropriate therapeutic decision-making are essential for optimizing outcomes in gallbladder perforation. While immediate surgical intervention is mandatory in Type I perforations, Type II and III perforations may initially be managed conservatively, with delayed surgery based on clinical indications.

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EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS – A FOUR-YEAR LONGITUDINAL FOLLOW-UP CASE REPORT

EOZINOFILNA GRANULOMATOZA SA POLIANGIITISOM – STUDIJA SLUČAJA SA ČETVOROGODIŠNJIM LONGITUDINALNIM PRAĆENJEM

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Abstract

Introduction. Eosinophilic granulomatosis with polyangiitis is a rare antineutrophil cytoplasmic antibody- associated small- to medium-vessel necrotizing vasculitis characterized by asthma, eosinophilia, and heterogeneous multisystem involvement. Diagnosis is based on a combination of clinical, laboratory, and histopathological findings, in accordance with current guideline-recommended criteria. Treatment strategies are stratified according to disease severity, with systemic glucocorticoids as first-line therapy and additional immunosuppressive agents reserved for relapsing or refractory disease. **Case Report.** We report the case of a 44-year-old woman with a history of asthma and chronic sinusitis who presented with rapidly progressive leg pain, paresthesias, cutaneous purpura, and constitutional symptoms. Laboratory investigations revealed marked leukocytosis with severe eosinophilia, anemia, elevated inflammatory markers, and strongly positive anti-myeloperoxidase antibodies. Electromyography demonstrated chronic sensorimotor polyneuropathy, while muscle biopsy confirmed acute necrotizing vasculitis. Cardiac involvement was excluded, and renal function and urinalysis remained normal. Given the severity of clinical manifestations, induction therapy with high-dose glucocorticoids and methotrexate was initiated, followed by a structured tapering regimen during outpatient follow-up. Over a four-year follow-up period, the patient achieved rapid clinical improvement, normalization of eosinophil counts, resolution of neuropathic and cutaneous manifestations, and sustained antineutrophil cytoplasmic antibodies negativity. Complete remission was maintained after discontinuation of both glucocorticoids and methotrexate, without evidence of relapse. **Conclusion.** This case illustrated that eosinophilic granulomatosis with polyangiitis without adverse prognostic factors can respond favorably to timely diagnosis and appropriately tailored immunosuppressive therapy. Early initiation of glucocorticoids combined with methotrexate, supported by structured monitoring and guided tapering, resulted in complete and sustained remission with full recovery of neurologic and cutaneous involvement. Durable remission following treatment withdrawal highlights the potential for long-term disease control in selected patients.

Key words: Granulomatosis with Polyangiitis; Churg-Strauss Syndrome; Vasculitis; Purpura; Peripheral Nervous System Diseases; Methotrexate

Sažetak

Uvod. Eozinofilna granulomatoza sa poliangiitisom predstavlja redak nekrotizujući vaskulitis malih i srednjih krvnih sudova asociran sa prisustvom antineutrofilnih citoplazmatskih antitela koji karakterišu astma, eozinofilija i heterogene kliničke manifestacije. Dijagnoza se zasniva na kliničkim, laboratorijskim i histopatološkim nalazima, tumačenim u skladu sa preporučenim kriterijumima. Terapija se određuje prema težini bolesti, pri čemu su glukokortikoidi terapija prvog izbora, a dodatni imunosupresivi se primenjuju kod relaps-refraktorne bolesti. **Prikaz slučaja.** Prikazana je 44-godišnja pacijentkinja sa istorijom astme i hroničnog sinusitisa, koja se klinički prezentovala progresivnim razvojem bola u nogama, parestezijama, pojavom purpuričnih papula i opštim konstitucionalnim simptomima. Laboratorijski nalazi su pokazali izraženu leukocitozu sa eozinofilijom, anemiju, povišene inflamatorne markere i pozitivnu antimijeloperoksidazu antitela. Elektromioneurografija je ukazala na hroničnu senzomotornu polineuropatiju, dok je biopsija mišića potvrdila akutni nekrotizujući vaskulitis. Isključena je kardiološka involucija. Bubrežna funkcija i nalaz urina bili su uredni. Na osnovu procene težine bolesti započeta je indukciona terapija visokim dozama glukokortikoida i metotreksata, uz postepeno i kontrolisano smanjivanje doze. Tokom četvorogodišnjeg praćenja postignuto je kliničko poboljšanje, normalizacija broja eozinofila, povlačenje neuropatskih i kožnih manifestacija i kontinuirana seronegativnost na antineutrofilna citoplazmatska antitela. Potpuna remisija je održana i nakon prekida glukokortikoida i metotreksata, bez zabeleženog relapsa. **Zaključak.** Ovaj slučaj pokazuje da eozinofilna granulomatoza sa poliangiitisom može dobro odgovoriti na blagovremenu dijagnozu i adekvatno prilagođenu imunosupresivnu terapiju. Rano uvođenje glukokortikoida i metotreksata, uz intenzivno praćenje i smanjivanje doze, rezultiralo je potpunom i održivom remisijom, uz potpuni oporavak neuroloških i kožnih manifestacija. Dugoročna stabilnost nakon prekida terapije potvrđuje da je trajna remisija dostižna kod ovih pacijenata.

Ključne reči: granulomatoza sa poliangiitisom; Čurg-Štraus sindrom; vaskulitis; purpura; periferna neuropatija; metotreksat

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Abbreviations

EGPA – eosinophilic granulomatosis with polyangiitis
ACR – American College of Rheumatology
EULAR – European Alliance of Associations for Rheumatology
ANCA – antineutrophil cytoplasmic antibodies
anti-MPO – anti-myeloperoxidase antibodies
HIV – human immunodeficiency virus
NCS – nerve conduction studies
ENT – ear, nose, and throat
FFS – Five-Factor Score

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic necrotizing vasculitis affecting small- to medium-sized blood vessels and extravascular granuloma formation [1,2]. The pathogenesis of EGPA is influenced by genetic and environmental factors [3]. Classically, the disease evolves through three phases, which may overlap and delay diagnosis [4]. Clinical spectrum of EGPA is broad and heterogeneous, influenced by antineutrophil cytoplasmic antibody (ANCA) status [5]. Common manifestations include constitutional symptoms such as fever, fatigue, and weight loss, cutaneous involvement such as palpable purpura, respiratory features including asthma and chronic rhinosinusitis, and involvement of the heart, kidneys, peripheral nerves, musculoskeletal system (arthralgia and myalgia), as well as hematologic and gastrointestinal disorders [2,6]. Diagnosis relies on a combination of clinical presentation, laboratory findings, and histopathological confirmation. Classification and diagnostic guidance are commonly based on the American College of Rheumatology (ACR) criteria and recommendations from the European Alliance of Associations for Rheumatology (EULAR) [1,2,7]. Treatment strategies for EGPA are tailored according to disease severity and the presence of adverse prognostic factors. Patients with non-severe disease are typically treated with glucocorticoid monotherapy, with a high likelihood of achieving remission [2,7]. In contrast, severe disease requires induction therapy with high-dose glucocorticoids combined with intravenous cyclophosphamide or rituximab, followed by maintenance therapy with methotrexate, azathioprine, or mepolizumab. Biologic agents play a central role in relapsing or refractory disease [2,8]. Supportive management also includes careful glucocorticoid tapering, structured follow-up using activity scores, infection prophylaxis, and monitoring for organ damage [1,7]. The aim of this report is to illustrate the clinical course, diagnosis, and successful long-term management of EGPA, emphasizing the importance of early diagnosis and individualized therapy in achieving sustained remission.

Case Report

A 44-year-old woman presented with a 10-day history of progressive lower-extremity symptoms. Initial complaints included pain and cramping in the calf muscles, followed by the gradual onset of heel, plantar, and toe pain. The symptoms progressed to the point that she was unable to climb stairs. During the same period, she developed bilateral ankle swelling. The skin over the lower legs became warm, erythematous, and pruritic. She also reported generalized fatigue, pain in the small joints of the hands, and shoulder pain exacerbates by arm movement. Her medical history was notable for long-standing chronic sinusitis, with persistent nasal obstruction and impaired nasal breathing. She denied recent asthma exacerbations and did not require increased use of maintenance therapy. Prior to admission to the Clinic for Nephrology and Clinical Immunology at the University Clinical Centre of Vojvodina, a complete blood count performed in primary care revealed marked leukocytosis with eosinophilia, accompanied by progressive clinical deterioration and fever up to 38 °C. Empirical antibiotic therapy was initiated. Soon thereafter, she developed intense pruritus around the ankles, leading to excoriations.

Pre-admission laboratory investigations, performed five days before hospitalization, showed white blood cells (WBC) count of 29.35×10^9/L with 41.9% eosinophils, microcytic anemia (Hb 90 g/L), and thrombocytosis (487×10^9/L). Inflammatory markers were elevated, with C-reactive protein (CRP) 76.8 mg/L and ESR 43 mm/h, while procalcitonin was only mildly increased (0.07). Basic metabolic panel, liver enzymes, coagulation parameters, and lipid profile were within reference ranges. Rheumatoid factor was negative. Urine sample was not obtained due to active menstruation. Family history was significant for paternal lung cancer.

Three days prior to admission, the patient was evaluated by a hematologist, started on prednisone 15 mg daily, and urgently referred to the nephrology and immunology department. On the same day, dermatologic examination revealed doughy edema of the ankles and several purpuric papules and plaques on the lower legs and dorsum of the feet **(Figure 1)**.

On admission, the patient was alert, oriented, and communicative. Lung auscultation revealed diffuse low-pitched wheezing. Cardiovascular and abdominal examinations were unremarkable. Physical examination of the lower extremities demonstrated mild pedal edema and pasty swelling of both ankles, with warm erythematous skin, excoriations over both malleoli, and palpable purpuric papules and plaques on the lower legs and dorsum of the feet. Repeat lab-

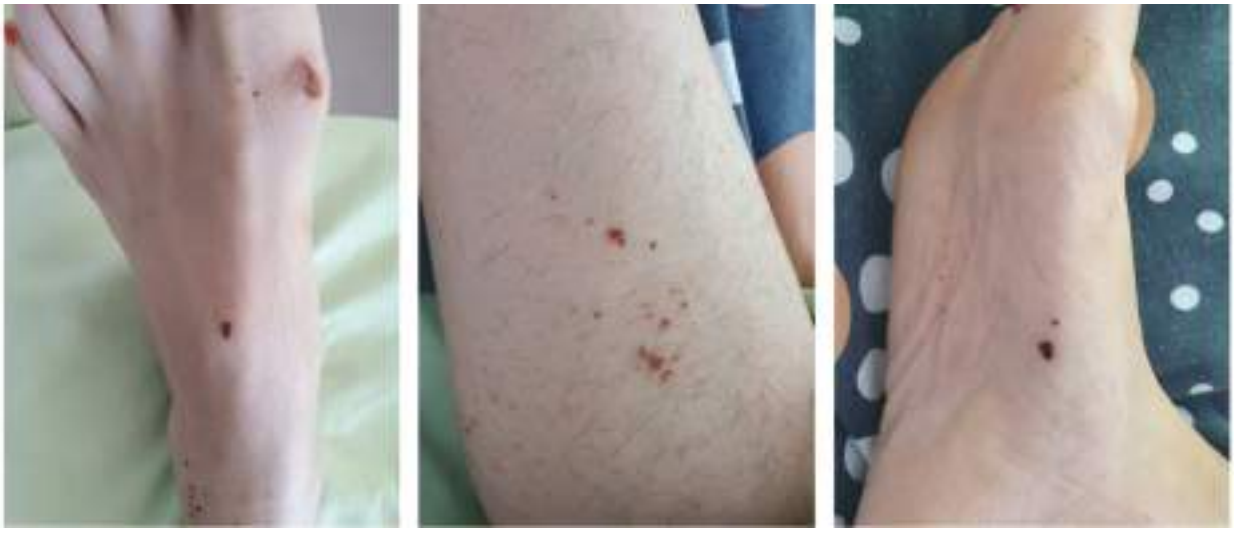
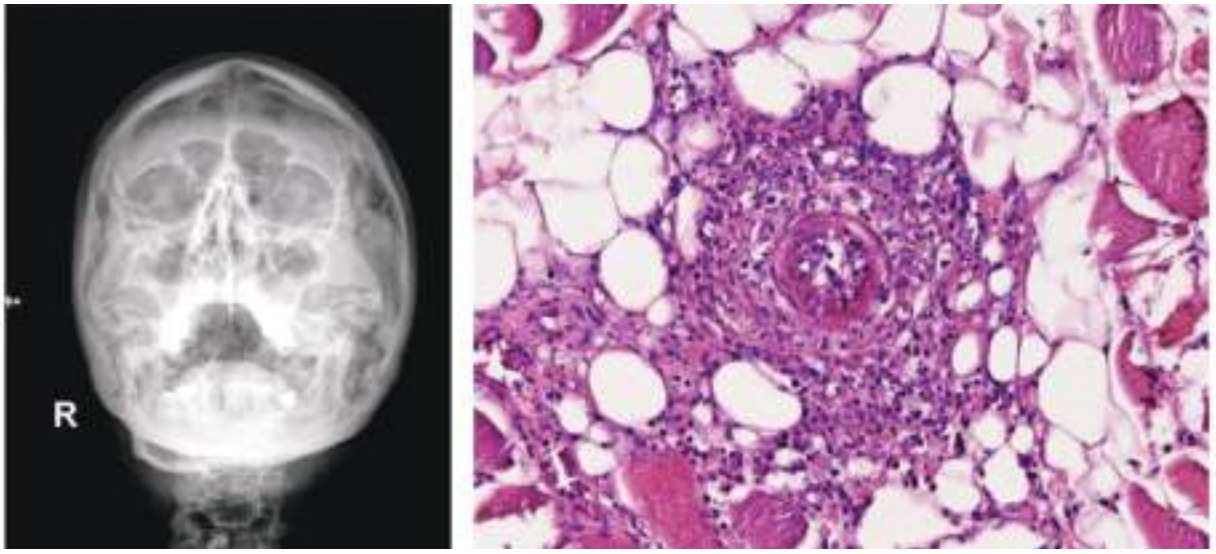


Figure 1. Palpable purpuric papules and plaques on the skin of the lower limbs

oratory testing on admission confirmed persistent leukocytosis (WBC 29.74 × 10^9/L) with 43.2% eosinophils, microcytic anemia (Hb 95 g/L), and thrombocytosis (533 × 10^9/L). Peripheral blood smear showed eosinophilia (44%), anisopoikilocytosis, hypochromia, microcytosis, and anulocytes. CRP was 29.1 mg/L, while procalcitonin had normalized (0.05). Renal function was preserved (creatinine 57 μmol/L; estimated glomerular filtration rate 100 mL/min/1.73 m^2). Iron studies demonstrated low serum iron (3.9 μmol/L) with normal ferritin levels. Immunoglobulin levels were within reference ranges, except for markedly elevated IgE (546 IU/mL). Complement level (C3 and C4) were normal, and the direct Coombs test was negative. Thyroid function tests were normal under replacement therapy. Autoantibodies revealed positive ANCA, with strongly positive anti-myeloperoxidase (Anti-MPO) antibodies (>100 AU/mL), while proteinase 3 (PR3) antibodies were negative. Rheumatoid factor was mildly elevated (74 IU/mL), whereas ANA and anti-cyclic citrullinated peptide (anti-CCP) antibodies were negative. Serologic testing for HIV and hepatitis viruses was negative. Urinalysis obtained during menstruation showed hemoglobin positivity with mild microscopic hematuria and no proteinuria. Repeated urinalysis after menstruation confirmed the absence of proteinuria and hematuria. Given the presence of iron-deficiency anemia, screening for occult gastrointestinal bleeding was performed and was negative. Gynecologic evaluation



Figures 2 and 3. Paranasal sinuses X ray showing mucosal thickening and normal sinuses transparency; Muscle biopsy histopathological analysis revealing acute vasculitis characterized by a dense mixed inflammatory infiltrate with some individual eosinophiles

revealed chronic cervicitis and two uterine myomas, considered the most likely cause of secondary sideropenic anemia. Vaginal flora analysis was unremarkable except for *Candida spp.* isolation. Urine culture and stool parasitological examination were negative. Electromyography (EMG) and nerve conduction studies (NCS) demonstrated chronic, moderately severe sensorimotor polyneuropathy, with absent sural nerve responses and reduced amplitudes in all examined motor nerves except the left peroneal nerve. Mildly slowed conduction velocity was noted in the right tibial nerve. Sinus radiography showed preserved aeration with mild mucosal thickening of the anterior paranasal sinuses **(Figure 2)**. Chest computed tomography revealed no pulmonary infiltrates; only a few bilateral micronodules were observed. There was no mediastinal or axillary lymphadenopathy, pleural effusion, or pericardial effusion. Cardiac ultrasound demonstrated normal chamber dimensions, intact valve morphology, preserved systolic and diastolic function, and no pericardial effusion. Histopathological examination of a skin biopsy revealed chronic superficial perivascular dermatitis. In contrast, muscle biopsy showed acute vasculitis, characterized by a dense mixed inflammatory infiltrate involving the vessel wall with focal vascular necrosis, consistent with active vasculitis **(Figure 3)**. The Five-Factors Score (FFS) was 0.

During hospitalization, induction therapy was initiated with high-dose prednisone (1 mg/kg) and methotrexate 10 mg weekly, along with folic acid supplementation, gastric protection, vitamin D, and B-complex vitamins due to the presence of polyneuropathy. At discharge, structured prednisone taper was prescribed, starting with 60 mg daily for 5 days, followed by 50 mg daily for 7 days, and then 40 mg daily until the first outpatient follow-up visit. Methotrexate was continued at 10 mg weekly, with folic acid 5 mg administered the day after methotrexate intake. Supportive therapy included pantoprazole 20 mg twice daily, vitamin D 2000 IU daily, and Milgamma (B-complex vitamins: B1, B6 and B12) twice daily.

Over a four-year follow-up period, patient demonstrated progressive and sustained clinical improvement. One month after discharge, neuropathic symptoms persisted, although eosinophil counts and inflammatory markers had substantially decreased under high-dose corticosteroid and methotrexate therapy. At subsequent outpatient visit, paresthesias gradually diminished and cutaneous lesions resolved. Inflammatory markers normalized, while mild anemia persisted. Eight months later, the patient reported only residual neuropathic discomfort. Eosinophil counts normalized (8%), inflammatory markers remained within reference limits, and ANCA serology converted to negative, allowing further tapering of prednisone.

Table 1. Timeline of visits with clinical status, key laboratory findings and treatment regimen

Time after discharge	Clinical status	Key laboratory findings	Treatment at the time
1 month	Improving; persistent neuropathic symptoms; skin lesions resolving	WBC 14.35 (Eos 28.9%); Hb 98; CRP 9; ESR 22	Prednisone taper (35→20 mg); MTX 12.5 mg/wk; supplements
4 months	Further improvement; reduced paresthesias; cushingoid	WBC 12.3 (Eos 19%); Hb 94; CRP 5, ESR 15	Prednisone 15→10 mg alt days; MTX 12.5 mg/wk
8 months	Stable; residual neuropathy only	WBC 9.2 (Eos 8%); Hb 100; CRP <5, ESR 7	Prednisone 10→5 mg alt days; MTX 12.5 mg/wk
12 months	Clinically stable; no new skin lesions	WBC 11.1 (Eos 8%); Hb 101; CRP <5, ESR 7, C3 nad C4 normal, ANCA negative	Prednisone 10–5 mg alt days; MTX 12.5 mg/wk
18 months	Improved; neuropathic pain resolved	WBC 10.2 (Eos 7%); Hb 111; CRP 8	Prednisone 5 mg; MTX 12.5 mg/wk
24 months	Asymptomatic	WBC 11.5 (Eos 11%); Hb 115; CRP 7, ESR 10, ANCA negative	Prednisone 5 mg qod; MTX 12.5 mg/wk
32 months	Asymptomatic	WBC 8.5 (Eos 7%); Hb 120; CRP <5, ESR 5,	Prednisone discontinued; MTX 12.5 mg/wk
40 months	Asymptomatic; patient self-discontinued MTX	WBC 7 (Eos 6%); Hb 121; CRP <5, ESR 8, C3 and C4 normal, ANCA negative	No immunosuppression supplements only
48 months	Stable; in full clinical remission without therapy	WBC 7 (Eos 7%); Hb 120; CRP <5, Iron 24 umol/L	None

WBC – white blood cell, Eos – eosinophils, Hb – hemoglobin, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, MTX – Methotrexate

Over the following nine months, the patient remained clinically stable, with complete resolution of neuropathic symptoms and no new vasculitic manifestations. Laboratory findings consistently showed normal eosinophil counts and persistent negative ANCA titers. Two years after hospitalization, the patient remained asymptomatic with laboratory results within reference ranges. Prednisone was discontinued after 30 months. Shortly thereafter, the patient independently discontinued methotrexate due to intolerance; nevertheless, she remained in sustained clinical and serological remission without relapse. Four years after the initial presentation, the patient remained off all immunosuppressive therapy, in complete clinical remission, with low inflammatory markers and stabilized hemoglobin level. A summary of laboratory findings, clinical status, and treatment during the four-year follow-up period is provided in **Table 1.**

Discussion

EGPA affects males and females at approximately equal rates, although some studies report a slight female predominance, particularly among patients presenting with asthma and ear, nose, and throat (ENT) involvement [6,9]. The clinical presentation of EGPA is highly heterogeneous [1,2], with manifestations often appearing at different times, which can delay recognition and result in diagnosis only after the disease has reached a more advanced stage [2]. The disease typically presents in mid-to-late adulthood, with a peak onset between 40 and 60 years of age [6,10], consistent with the age of our patient. Classically, EGPA evolves through prodromal, eosinophilic, and vasculitic phases; however, these stages often overlap, further complicating timely diagnosis [4,11]. The **prodromal phase** is characterized by asthma, allergic rhinitis, and chronic sinusitis, often persisting for many years and frequently accompanied by ENT manifestations [1,12]. This pattern was evident in our patient, who had been treated for bronchial asthma and chronic sinusitis for over 20 years. The patient presented with rapidly progressive lower-extremity symptoms, including pain, cramping, and paresthesias. Neurological involvement in EGPA commonly manifests as distal symmetric polyneuropathy with paresthesia, numbness, and weakness [13,14]. In addition, ankle swelling, small joint pain of the hands, and shoulder pain exacerbated by arm elevation have been described in the literature as a common presentation of EGPA [15]. Matucci et al. reported that up to 20% of patients exhibit arthritis [16]. Purpura is the most common cutaneous lesion in EGPA [2,13,15]. Kataoka and al. demonstrated that purpura is associated with elevated CRP and IL-5 levels, reflecting higher disease activity [17]. Anemia is a relatively common finding in EGPA, however, other causes such as hemolytic anemia or lymphoma should be excluded due to its complex pathophysiology [18]. In our patient, an extensive workup – including peripheral blood smear analysis, Coombs testing, lactate dehydrogenase (LDH) and bilirubin measurements - excluded hemolysis. Gynecological evaluation revealed two myomas and increased menstrual bleeding, identifying chronic blood loss as the most likely cause of microcytic anemia. This condition was likely further exacerbated by inflammation during the EGPA flare [19]. Immunoglobulin levels were within reference ranges except for markedly elevated Immunoglobulin E (546 IU/mL), with a characteristic finding in EGPA, reflecting the underlying Th2-driven eosinophilic and allergic immune response [13]. Given that ANCA-positive patients (strongly positive Anti-MPO>100 AU/mL in our patient) are more prone to vasculitic manifestations such as glomerulonephritis [2,14], renal involvement was carefully assessed, including 24-hour proteinuria measurement, along with multiple analyses of urine and serum urea, creatinine, and uric acid levels, all of which were within normal ranges. Durel et al. reported renal involvement in approximately 25–30% of EGPA patients [20]. Infectious screening for HIV and hepatitis viruses was performed prior to the initiating therapy, as rare associations between chronic viral infections and EGPA have been reported [21]. EMG and NCS confirmed chronic, moderately severe sensorimotor polyneuropathy, characterized by absent sural nerve responses and reduced motor amplitudes in all tested nerves except the left peroneal nerve, a pattern well described in EGPA-related neuropathy [2,14]. In addition to general recommendations, Liu and Srikhantharajah [3,24] highlighted cardiac involvement in EGPA, comprehensive echocardiographic evaluation was performed and showed no abnormalities. Pulmonary imaging revealed no evidence of interstitial lung disease typically seen in hypereosinophilic syndromes [22]. Radiographic evaluation of the paranasal sinuses demonstrated mucosal thickening with preserved sinus transparency, consistent with chronic sinusitis [23]. Histopathological description of tissue samples consisted of neutrophilic infiltrate with abundant eosinophils, vascular wall necrosis and vasculitis, as reported by several authors [24]. In our case, findings were consistent with active vasculitis. Given the absence of adverse prognostic factors (Five-Factor Score (FFS) = 0) and lack of life-threatening organ involvement, induction therapy was initiated with prednisone (1 mg/kg/day) combined with methotrexate (10 mg once weekly), with a planned increase to 12.5 mg weekly

depending on drug tolerability. According to EULAR recommendations, methotrexate is an appropriate option for remission maintenance following glucocorticoid-induced remission is in patients with EGPA [2,7]. Although glucocorticoid monotherapy induced remission in more than 90% of such patients, relapse during dose tapering is common [7], prompting many clinicians to combine glucocorticoids with additional immunosuppressive or biologic agents. While evidence supporting methotrexate or mycophenolate mofetil remains limited – owing to small observational studies and a lack of randomized control trails – methotrexate has demonstrated favorable outcomes in several small cohorts and is widely used as a steroid-sparing agent in non–severe EGPA [2,19]. In our patient, early glucocorticoid tapering was performed in accordance with EULAR [7] guidelines once clinical remission and biomarker improvement were achieved, minimizing long-term toxicity. Sustained remission, normalization of eosinophil counts, and persistent ANCA negativity supported complete glucocorticoid discontinuation, consistent with current guidelines advocating the lowest effective cumulative exposure [2,7,19]. Babapoor et al. indicate that approximately 72% of patients with ANCA-associated vasculitis achieving long-term remission following induction therapy, with nearly 38% remaining off all medications [25]. Remarkably, despite the patient's independent discontinuation of methotrexate due to intolerance, she remained in complete clinical and serological remission one year later.

Conclusion

Eosinophilic granulomatosis with polyangiitis is a rare systemic necrotizing vasculitis characterized by highly heterogeneous clinical manifestations. This four-year longitudinal follow-up demonstrates that the disease can be effectively controlled through early diagnosis and individualized treatment guided by disease severity and prognostic scoring. In the present case, induction therapy with high-dose glucocorticoids combined with methotrexate resulted in rapid disease control, normalization of eosinophil counts, resolution of organ-specific manifestations, and sustained clinical and serological remission. Careful tapering of glucocorticoids minimized cumulative exposure, while methotrexate served as an effective steroid-sparing agent. Medication-free remission was maintained even after methotrexate discontinuation, underscoring the potential for long-term disease control. These findings highlight the importance of early recognition, close monitoring, and guideline-driven, individualized therapy in optimizing long-term outcomes for patients with eosinophilic granulomatosis with polyangiitis.

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CASE REPORTS
PRIKAZI SLUČAJEVA

PERINEURAL METASTASIS OF CUTANEOUS SQUAMOUS CELL CARCINOMA OF THE NOSE AND PERIOCULAR REGION – A CASE REPORT

PERINEURALNO METASTAZIRANJE KUTANOG SKVAMOCELULARNOG KARCINOMA NOSA I PERIOKULARNE REGIJE – PRIKAZ SLUČAJA

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Case report
Prikaz slučaja
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Abstract

Introduction. Cutaneous squamous cell carcinoma is the second most common malignant skin tumor and predominant affects the head and neck region. Although most cases have a favorable outcome following surgical excision, high-risk tumors—particularly those exhibiting perineural invasion—are associated with aggressive behavior, local recurrence, and metastatic spread. **Case Report.** We present the case of a 66-year-old woman with high-risk cutaneous squamous cell carcinoma of the nose and glabellar region. Clinical examination and computed tomography demonstrated full-thickness involvement of the nasal pyramid, with destruction of the cartilaginous septum and the right nasal bone. The patient underwent total nasal amputation with R0 resection and local reconstruction. Histopathological analysis revealed a keratinizing squamous cell carcinoma with marked perineural invasion. Although adjuvant radiotherapy was indicated, the patient declined further treatment. Three months after surgery, she developed an orbital metastatic lesion manifesting by ptosis and periorbital swelling. The patient subsequently died due to acute intracranial hemorrhage. **Conclusion.** This case illustrates the aggressive nature of high-risk cutaneous squamous cell carcinoma with perineural invasion and its potential for rapid metastatic progression despite complete surgical resection. Early identification of histopathological risk factors and timely implementation of adjuvant oncologic therapy are crucial for improving outcomes in patients with perineural invasive cutaneous tumors.

Key words: tumori kože; skvamozni karcinom; nos; metastaza; invazivnost tumora; faktori rizika; ishod lečenja

Sažetak

Uvod. Skvamocelularni karcinom kože je drugi najčešći maligni tumor kože, sa dominantnom lokalizacijom u regiji glave i vrata. Iako većina tumora ima povoljan tok nakon hirurške ekscizije, visokorizične forme, naročito one sa perineuralnom invazijom, pokazuju sklonost ka lokalnoj recidivnosti i metastaziranju. **Prikaz slučaja.** Prikazana je pacijentkinja starosti 66 godina sa visokorizičnim skvamocelularnim karcinomom kože nosa i glabelarne regije. Kliničkim i radiološkim pregledom kompjuterizovanom tomografijom, tumor je zahvatao punu debljinu nosne piramide sa destrukcijom hrskavičavog septuma i desne nosne kosti. Učinjena je totalna amputacija nosa sa R0 resekcijom i lokalnom rekonstrukcijom. Patohistološki je potvrđen keratinizujući planocelularni karcinom sa izraženom perineuralnom invazijom. Iako je adjuvantna radioterapija bila indikovana, pacijentkinja ju je odbila. Tri meseca nakon operacije razvila je metastatsku leziju orbite sa kliničkom slikom ptoze i periorbitalnog otoka. Kratko nakon toga preminula je usled akutne intrakranijalne hemoragije. **Zaključak.** Ovaj slučaj ilustruje agresivan tok visokorizičnog skvamocelularnog karcinoma kože sa perineuralnim metastaziranjem i brzom progresijom bolesti uprkos kompletnoj resekciji. Rano prepoznavanje histoloških faktora rizika i sprovođenje adjuvantnog onkološkog lečenja od suštinskog su značaja za poboljšanje ishoda kod pacijenata sa perineuralno invazivnim tumorima kože.

Ključne reči: Skin Neoplasms; Carcinoma, Squamous Cell; Nose; Neoplasm Metastasis; Neoplasm Invasiveness; Risk Factors; Treatment Outcome

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin malignancy, with more than 80% of cases occurring in the head and neck region. It belongs to the group of non-melanoma skin cancers, which collectively account for approximately one-third of all malignant tumors worldwide [1,2]. The most important etiological factor is cumulative damage from chronic ultraviolet (UV) radiation exposure. Advanced aid and immunosuppression significantly increase the risk of disease development and progression [1,3].

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Abbreviations

AJCC – American Joint Committee on Cancer
BWH – Brigham and Women's Hospital (prognostic staging system for cSCC)
cSCC – Cutaneous Squamous Cell Carcinoma
CT – computed tomography
HG1 – Histologic Grade 1 (well-differentiated carcinoma)
IMRT – intensity-modulated radiotherapy
MRI – magnetic resonance imaging
NCCN – National Comprehensive Cancer Network
PD-1 – Programmed Death-1 (immune checkpoint receptor)
PNI – perineural invasion
R0 – complete surgical resection with negative margins
VMAT – Volumetric Modulated Arc Therapy

Case Report

A 66-year-old woman presented with a *de novo* tumor lesion on the skin of the nose that had first appeared approximately seven months earlier. Since its onset, the lesion had progressively enlarged and was associated with intermittent bleeding. Three months after the initial lesion development, the patient noticed a second, similar lesion on the skin of the nasal root above the right eye. Her medical history was notable for surgically treated –uterine adenocarcinoma 13 years earlier, without evidence of recurrence. She denied alcohol consumption, tobacco use, or exposure to psychoactive substances. The patient was retired, but had previously worked in agriculture, with long-term occupational exposure to ultraviolet radiation.

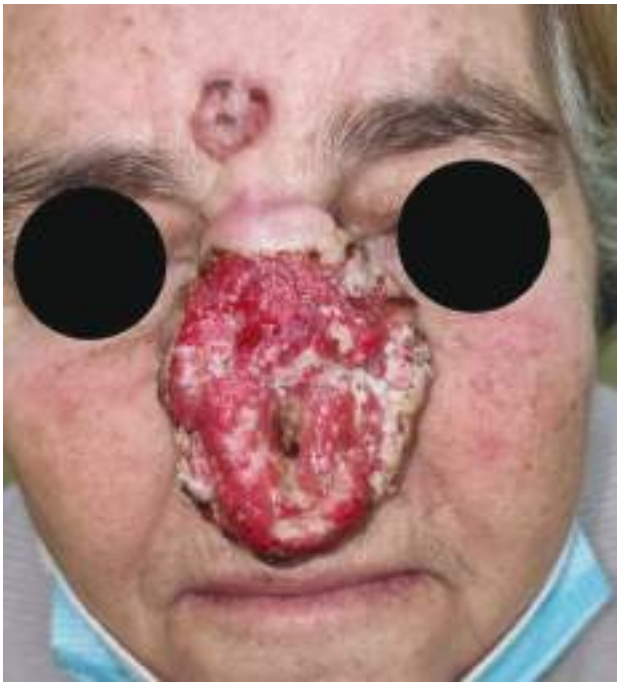

Figure 1. Preoperative condition

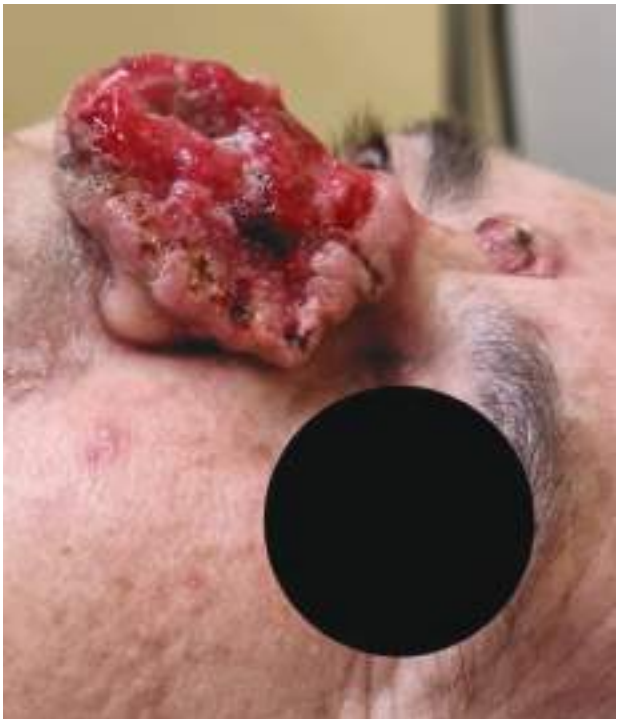

Figure 2. Preoperative condition - profile

On physical examination, an exophytic, irregular tumor mass measuring approximately 4 cm in diameter was observed, completely covering the nasal pyramid and exhibiting surface ulceration **(Figures 1 and 2).** Endonasal examination revealed full-thick-

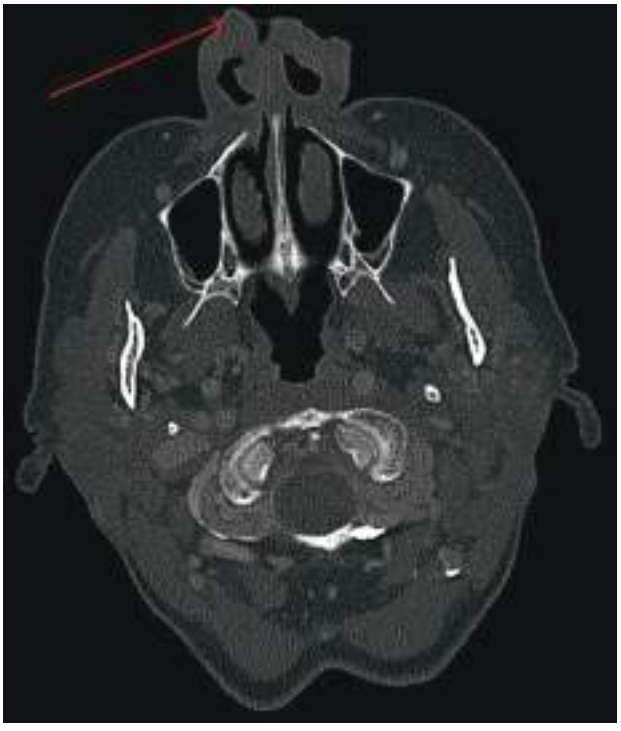

Figure 3. CT scan of the head - tumoral change and involvement of the soft tissues of the nose - indicated by an arrow

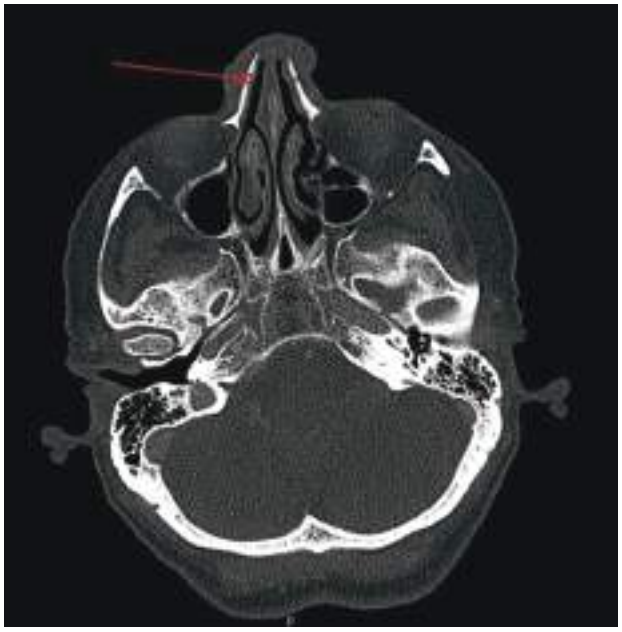

Figure 4. CT scan of the head - tumoral change and involvement of the bony structures of the nose - indicated by an arrow

Figure 5. Postoperative condition - 10 days after surgery

ness infiltration of the nasal alae and columella, with extension to the nasal mucosa and destruction of the cartilaginous septum, which was partially exposed on the dorsal aspect of the nose. Additionally, an oval tumor lesion measuring 12 mm in diameter was present in the glabellar region. This lesion was elevated above the skin surface, with undermined borders and central necrosis, and showed no continuity with the primary nasal tumor **(Figure 1).** Multislice computed tomography (CT) of the facial bones, paranasal sinuses, and brain demonstrated infiltration of the full thickness of the nasal skin, alae, columella, cartilaginous septum, and right nasal bone, without evidence of invasion into adjacent facial structures or

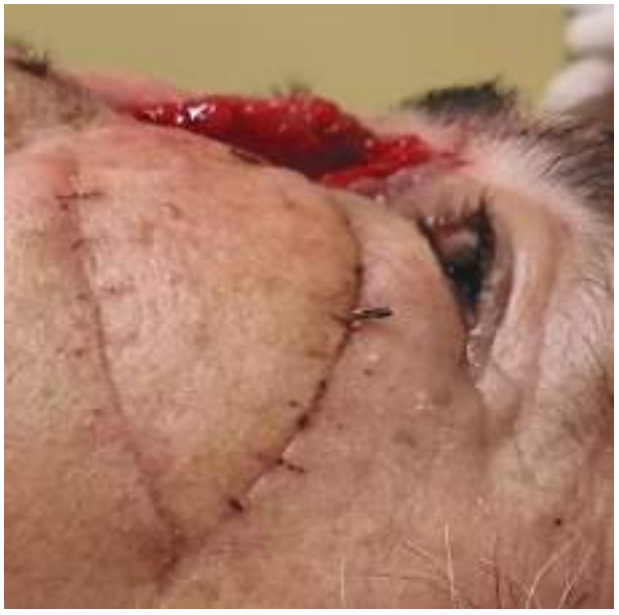

Figure 6. Postoperative condition - 10 days after surgery - profile

intracranial extensions **(Figures 3 and 4).** Ultrasonography of the regional lymph node basins revealed no enlarged or morphologically suspicious lymph nodes. The patient underwent total nasal amputation with resection of the involved portions of the right nasal bone and cartilaginous septum, as along with excision of the glabellar lesion using a 10-mm safety margin. Reconstruction of the glabellar and infraorbital defects was performed using local V-Y advancement flaps, while the defect created by removal of the nasal pyramid in the region of the piriform aperture was left to heal by secondary intention (*per secundam intentionem*) **(Figures 5 and 6).** The postoperative course was uneventful, apart from minor periorbital hematomas. Two weeks after surgery, complete wound healing was achieved, with progressive marginal epithelialization of the piriform aperture defect. Histopathological examination revealed *carcinoma planocellulare keratodes exulceratum et infiltrativum* involving the skin and fibrous, adipose, muscular, chondroid tissues, as well as the perineural space (HG1). All resection margins were free of tumor tissue, confirming an R0 resection) Adjuvant radiotherapy was recommended postoperatively, but the patient declined further treatment. Three months later, she developed swelling in the region of the right medial canthus accompanied by ptosis of the right upper eyelid. Magnetic resonance imaging (MRI) of the head revealed a metastatic lesion involving the orbital roof, with infiltration of the eyeball and eyelid. Two weeks thereafter, the patient died from acute intracranial hemorrhage. Autopsy

confirmed the presence of a 14-mm metastatic tumor in the right orbit, which had extended into the anterior cranial fossa, eroded the ophthalmic artery, and caused fatal intracranial bleeding. Histopathological analysis confirmed the lesion as a metastasis of squamous cell carcinoma.

Discussion

Surgical excision remains the gold standard in the treatment of cSCC. Despite generally favorable outcomes following complete excision, local recurrence occurs in approximately 3–5% of cases, metastatic disease develops in 3-16%, and disease-specific mortality ranges from 1.5–7.7% [3]. Tumors located on the ear, nose, lips, and temporal region exhibit higher rates of both metastasis and local recurrence. Histopathological parameters defining low- and high-risk tumor types include resection margin status, tumor size, depth of invasion, degree of differentiation, and the presence of perineural invasion [1,3,4]. According to both the AJCC and BWH staging systems, the tumor presented patient in this case fulfilled multiple high-risk criteria, including tumor diameter greater than 2 cm, thickness exceeding 2 mm, invasion of subcutaneous fat, cartilage and bone involvement, and extensive perineural invasion [1]. Although surgical margins were negative and consistent with European guideline recommendations for cSCC management [5], the cumulative presence of these adverse features indicated an aggressive tumor phenotype with a high probability of metastasis and local recurrence, associated with reduced overall survival [3,4,6,7]. Given the high-risk features, adjuvant radiotherapy was indicated postoperatively in accordance with National Comprehensive Cancer Network (NCCN) guidelines [7]. Perineural invasion (PNI) represents a particularly ominous histopathological finding and is defined as tumor cell infiltration with the perineural space, typically involving at least one-third of the nerve circumference. Immunohistochemical staining with pancytokeratin and S-100 protein is instrumental in confirming even subtle PNI, which may otherwise be misinterpreted as perineural inflammation on routine hematoxylin-eosin staining [8]. A distinctive and clinically significant characteristic of perineural spread is its discontinuous pattern: tumor cells may skip nerve segments, leaving intervening regions apparently uninvolved while progressing proximally along neutral pathways [4]. This biological behavior explains the use of adjuvant radiotherapy in high-risk tumors with PNI, even after R0 resection. Tumors of the periocular and eyelid region are associated with particularly aggressive behavior, demonstrating higher rates of lymphatic dissemination and perineural spread [9]. While adjuvant radiotherapy significantly improves local control and disease-free survival in high-risk cSCC, its use in the periocular region must be carefully balanced against the potential risk of vision impairment [8]. Modern conformal radiotherapy techniques, such as intensity modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT), allow for excellent sparing of adjacent organs and minimize risk of exposure to radiation of organs at risk [10,11]. Proton therapy, in particular, is recommended for head and neck malignancies due to the close proximity of organs at risk, and provides even better result [12,13]. These treatment options should be thoroughly discussed with patients in the adjuvant setting, given the strong evidence supporting their role in high-risk disease. In the present case, therapeutic options became limited due to rapid disease progression and the patent's refusal of adjuvant treatment. According to current standards, immunotherapy with PD-1 inhibitors represents the treatment of choice for unresectable, locally advanced, or metastatic cSCC. Cemiplimab and pembrolizumab are the two approved agents in this setting, with cemiplimab most commonly used as first-line therapy. These agents have demonstrated durable responses and significant survival benefits in cSCC [6,8,14,15]. Unfortunately, in this patient, further oncological treatment was declined due to severe psychological distress and loss of therapeutic motivation.

Conclusion

This case illustrates the markedly aggressive clinical behavior of cutaneous squamous cell carcinoma of the nose with perineural invasion and metastatic spread, despite complete surgical excision with negative margins. The presence of extensive perineural invasion and deep tissue infiltration underscores the critical importance of identifying high-risk histopathological features and implementing adjuvant oncologic therapy when indicated. Early recognition of aggressive tumor variants, multidisciplinary treatment planning, and close postoperative surveillance are essential to improving outcomes in patients with high-risk cutaneous squamous cell carcinoma.

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SOLITARY RECTAL ULCER SYNDROME – A CASE REPORT AND LITERATURE REVIEW – DIAGNOSTIC AND THERAPEUTIC PITFALLS

SINDROM SOLITARNOG REKTALNOG ULCERA – PRIKAZ SLUČAJA I PREGLED LITERATURE – DIJAGNOSTIČKA I TERAPIJSKA ZAMKA

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Case report
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Abstract

Introduction. Solitary rectal ulcer syndrome typically presents as painful or difficult defecation and rectal bleeding. The aim of this case report is to highlight how misinterpretation of histopathological findings following colonoscopy can lead to unnecessary and potentially mutilating surgical interventions. **Case Report.** A 58-year-old man was diagnosed with rectal cancer based on histopathological findings obtained after colonoscopy and supported by pelvic magnetic resonance imaging. A transanal excision of the suspected tumor mass was performed. However, definitive histopathological analysis of the surgical specimen revealed features consistent with solitary rectal ulcer syndrome. Subsequent revision of the initial colonoscopic biopsy by an experienced colorectal pathologist confirmed the diagnosis of solitary rectal ulcer syndrome. Follow-up colonoscopy performed three months postoperatively showed no evidence of tumors, ulcerations or polyps in the colon. **Conclusion.** Careful integration of clinical presentation, endoscopic findings, imaging, and expert histopathological evaluation is essential to avoid misdiagnosis and overtreatment. In suspected cases of solitary rectal ulcer syndrome, biopsy specimens should be reviewed by pathologists experienced in colorectal pathology do prevent unnecessary radical surgical procedures.

Key words: Rectal Diseases; Ulcer; Rectum; Gastrointestinal Hemorrhage; Colonoscopy; Biopsy; Treatment Outcome; Diagnostic Errors; Diagnosis

Sažetak

Uvod. Solitarni rektalni ulkus karakteriše bolna i otežana defekacija praćena rektoragijom. Cilj ovog prikaza slučaja je da pokaže kako pogrešna dijagnoza zasnovana na patohistološkom nalazu dobijenom nakon kolonoskopije može dovesti do izuzetno mutilantnih hirurških intervencija. **Prikaz slučaja.** Pedesetosmogodišnji pacijent sa inicijalnom dijagnozom karcinoma rektuma te nakon obavljene onkološke komisije za tumore kolorektuma donesena odluka o izvođenju amputacije rektuma, s obzirom na nalaze patohistološke analize i magnetne rezonance male karlice. Urađena je transanalna ekscizija tumora, a nakon definitivne patohistološke analize postavljena je dijagnoza sindroma solitarnog rektalnog ulkusa. Nakon revizije patohistološkog nalaza preparata dobijenog na kolonoskopiji, iskusni patolog je potvrdio dijagnozu dobijenu na operativnom materijalu. Kontrolna kolonoskopija je urađena tri meseca nakon operacije, a pacijent je bio bez prisustva tumora, ulceracija ili polipa u kolonu. **Zaključak.** Pažljivim pristupom svim anamnestičkim podacima kao i fizikalnim pregledom, te uvidom u ostale nalaze, može se izbeći prekomerni hirurški tretman pacijenata. U slučajevima rektalnog ulkusnog sindroma

Ključne reči: bolesti rektuma; uklus; rektum; gastrointestinalno krvarenje; kolonoskopija; biopsija; ishod lečenja; dijagnostičke greške; dijagnoza

Introduction

Solitary rectal ulcer syndrome (SRUS) was first described by Cruveihier in 1820s as a chronic disorder affecting of the rectal mucosa [1]. Despite its name, SRUS does not always present as a solitary lesion or an ulcer. The clinical and endoscopic spectrum ranges from erythematous mucosal changes to polypoid lesions and well-developed ulcers. These lesions are most commonly located 4-10 cm from the anocutaneous line (ACL) [1–4].

The pathogenesis of SRUS remains incompletely understood; however, several predisposing factors have been implicated, including prolonged straining during defecation, chronic constipation, and anatomical abnormalities of the rectum [4,5]. The estimated incidence is approximately one case per 100,000 individuals per year, with predominance in females [1–3]. SURS most commonly affects patients in the third and fourth decades of life.

The term *mucosal prolapsed syndrome* has been proposed as a more accurate designation, as the condition is not invariably rectal, ulcerative, or solitary. Clinically, SRUS is characterized by painful or difficult defecation, a sensation of incomplete evacuation, constipation, and rectal prolapse. Notably, up to 26% of patients may be asymptomatic. Lower gastrointestinal bleeding occurs in approximately 56%

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Abbreviations

SRUS – solitary rectal ulcer syndrome
ACL – anocutaneous line
HP – histopathological
EUS – endoscopic ultrasound

of cases, excessive straining during defecation 28%, and pelvic fullness in 23%, all of which may lead to misdiagnosis as inflammatory bowel disease or rectal malignancy [1–6].

Diagnosis relies on a combination of clinical presentation, endoscopic appearance, and histopathological (HP) evaluation. As clinical and endoscopic findings are often nonspecific, definitive diagnosis depends on characteristic HP features, including surface serration, fibromuscular obliteration, crypt distortion, and vascular abnormalities [5,7].

The aim of this case report is to demonstrate how an incorrect histopathological diagnosis following colonoscopic biopsy can result in unnecessary and potentially mutilating surgical treatment.

Case Report

A 58-year-old man was admitted to the Department of Surgery at the Oncology Institute of Vojvodina with a three-month history of progressively worsening symptoms, including intermittent abdominal pain, rectal bleeding, and a persistent sensation of incomplete evacuation. The rectal bleeding was painless, fresh, and mixed with stool. The patient reported chronic constipation and regular use oral laxatives. He had experienced an unintentional weight loss of approximately 6 kg over the preceding six months. The patients had no personal history of diabetes mellitus, hypertension, allergic reactions, or previous anorectal surgery. Family history was negative of gastrointestinal malignancies.

Digital rectal examination revealed no palpable rectal tumors, hemorrhoids, or fissures. A nonspecific, slightly protruding firmness was palpated on the posterior rectal wall.

Colonoscopy was recommended and subsequently performed at an external institution. Retroversion revealed a tumor-like mass measuring approximately 3 cm in diameter, located 2 cm from the ACL on the posterior rectal wall. Biopsy samples were obtained, and HP reported rectal adenocarcinoma (G2) with a mucinous component of approximately 20% **(Figure 1).** Neither the colonoscopy not the histopathological analysis was performed at the Oncology Institute of Vojvodina.

Further staging included chest and abdominal computerized tomography, which showed no evidence of distant metastases. Pelvic magnetic resonance imaging demonstrated a 15 mm lesion infiltrating the perirectal tissue, located 2 cm from ACL, adjacent to but not infiltrating the anal sphincters (radiological stage T1N0M0). Several perirectal lymph nodes were enlarged but without radiological features suggestive of malignant involvement. Tumor markers (CEA and CA 19-9) were within reference ranges. Based on these findings, the multidisciplinary oncology team initially recommended surgical treatment in the form of rectal amputation.

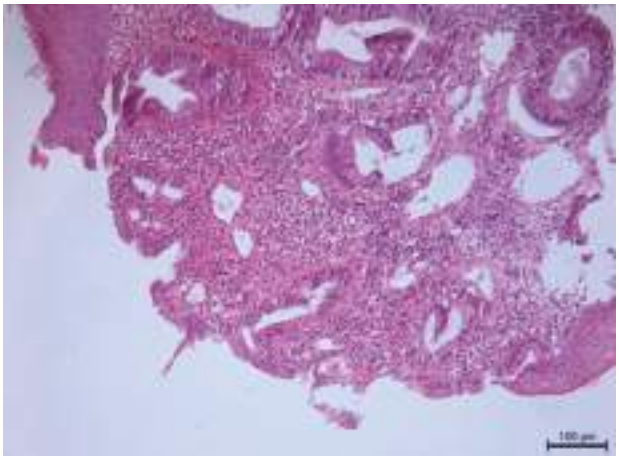

Figure 1. Histopathological findings of colonoscopic biopsy
Solitary rectal ulcer syndrome, H&E x 20. (Biopsy specimen demonstrating ulcerated surface of anorectal mucosa. Cryptal hyperplasia with dilatation is present, with moderate ectatic capillaries and inflammatory infiltrate.)

A transanal excision of the lesion was performed, and the surgical specimen was submitted for frozen-section analysis to assess the deep resection margin. HP examination revealed low- and high- grade dysplasia of the rectal mucosa. Gross examination showed a flattened, ulcerated mucosal area. Microscopic analysis demonstrated ulceration with prominent fibromuscular hyperplasia and thickening of the muscularis mucosae. Crypt distortion was mild, inflammatory infiltrate was minimal, and ectatic capillaries were conspicuous. These findings were consistent with solitary rectal ulcer syndrome **(Figures 2A and 2B).**

Following this result, the original colonoscopic biopsy was evaluated by an experienced colorectal pathologist. Revision of the specimen confirmed the diagnosis of SRUS. Histology revealed an ulcerated anorectal mucosal surface with distorted crypts lined by hyperplastic colonic epithelium. The lamina propria was thickened, with discrete fibromuscular hyperplasia and ectatic blood vessels. A moderate inflammatory infiltrate composed of lymphocytes and plasma cells was present, with no evidence of dysplasia **(Figure 1).** Consequently, the diagnosis of rectal cancer was definitely excluded.

Follow-up colonoscopy performed three months postoperatively showed no evidence of tumors, ul-

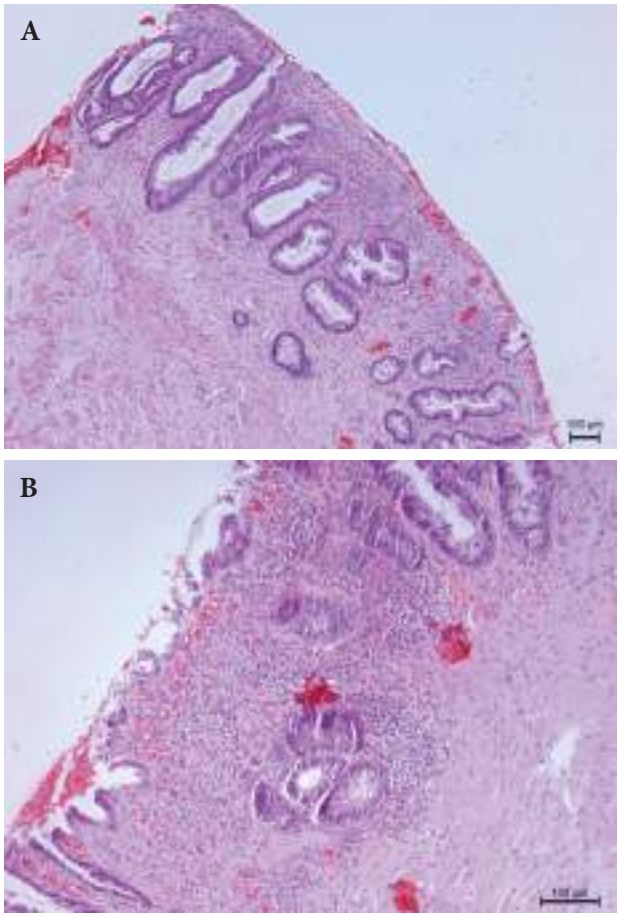

Figure 2 (A, B). Histopathological findings of the surgical specimen

Solitary rectal ulcer syndrome, H&E x 10. (Operative specimen confirming ulcerated surface with irregular crypts lined with hyperplastic epithelium. Muscularis propria is thickened and fibromuscular hyperplasia is present. Ectatic capillaries are marked and inflammation is mild.)

cerations, or polyps. At one-year follow-up, the patient remained asymptomatic.

Discussion

The etiology and pathophysiology of this rare benign disorder remain incompletely understood, and the clinical presentation of SRUS is notably heterogeneous. Three main hypotheses have been proposed to explain its pathophysiology. The first suggests that chronic mechanical trauma and local ischemia of the rectal mucosa - resulting from prolonged straining, constipation, tenesmus, intussusception, and chronic inflammation may play a central role in mucosal injury and ulcer formation [6–8]. The second hypothesis implicates paradoxical contraction of the puborectalis muscle during defecation, a feature commonly observed in patients with pelvic floor dyssynergia. This abnormal contraction may contribute to overt or occult rectal prolapse over time, leading to repetitive ischemic injury and mucosal ulceration. Although paradoxical puborectalis contraction can also be observed in healthy individuals, anorectal physiology studies have demonstrated dyssynergia in approximately 25–82% of patients with SRUS, supporting its role in disease development [8]. The third hypothesis proposes abnormal defecation dynamics caused by a reversed pressure gradient generated by inappropriate contraction of the external anal sphincter during evacuation [6–8].

SRUS is a well-recognized clinical and endoscopic mimicker of serious colorectal diseases, particularly rectal carcinoma and inflammatory bowel diseases. Endoscopic findings vary widely and may include erythematous patches, solitary or multiple ulcers, and non-ulcerative polypoid or mass-like lesions that closely resemble rectal malignancy of inflammatory bowel disease [1–3,6,8]. Lesions vary in size and location but are most commonly up to 4 cm in diameter and located on the anterior rectal wall [8]. In contrast, the lesion in our patient measured 15 mm and was located on the posterior rectal wall, highlighting the variability of SRUS presentation. Clinically, the classic symptom triad consists of rectal bleeding, constipation, and abdominal pain.

Several studies have suggested that endoscopic ultrasound (EUS) may be superior to MRI in the diagnostic evaluation of SRUS [9,10]. Typical EUS findings include thickening of the rectal wall and internal anal sphincter, mucosal intussusception, submucosal cysts, hyperechogenic fibrotic bands within the submucosa, and regional lymph node enlargement. Additionally, a reduced ratio of external to internal anal sphincter thickness has been reported in patients with SRUS [11].

HP examination remains the cornerstone of diagnosis. Characteristic features include fibromuscular obliteration of the lamina propria, hypertrophy and disorganization of the muscularis mucosae, and distorted crypt architecture. The most commonly reported HP findings include superficial ulceration (59%), crypt distortion (17%), and inflammatory infiltrated (33%) [3,8]. These changes reflect chronic mucosal injury and regenerative processes. Importantly, collagen disposition within the lamina propria is a key feature distinguishing SRUS from inflammatory bowel disease and chronic ischemic colitis [12]. Malignant lesions may initially present as superficial ulcers or polypoid masses; therefore, adequate biopsy and expert pathological interpretation are essential to exclude neoplastic infiltration. Although colonoscopy is indispensable for diagnosis, our case clearly demonstrated that misdiagnosis of biopsy specimens can lead to an incorrect diagnosis and potentially devastating overtreatment.

Management of SRUS begins with patient education and behavioral modification, which represent the foundation of therapy. Patients should be instructed in proper defecation techniques, including relaxation of the pelvic floor and external anal sphincter during evacuation. In selected cases, Kegel exercises may be beneficial [3]. Additional behavioral measures include a high-fiber diet, smoking cessation, adequate hydration (at least two liters of water daily), regulation of toilet habits, treatment of underlying psychological disorders, and avoidance of excessive straining or digital evacuation [13]. Patients with persistent or severe symptoms may require medical or surgical intervention. Topical therapies such as sucralfate, 5-ASA, sulfasalazine, and corticosteroid enemas have been reported to reduce inflammation and preventing irritant injury [1–15]. Surgical treatment is reserved for refractory cases and includes procedures such as rectopexy for rectal prolapse, the Delorme procedure for mucosal resection, or perirenal proctectomy (Altemeier procedure) [1–3,6,8,16].

Conclusion

A careful and systematic evaluation of clinical, endoscopic, radiological, and histopathological data is essential to avoid diagnostic errors and unnecessary surgical overtreatment in patients with solitary rectal ulcer syndrome. This case underscores the clinical importance of expert histopathological assessment by experienced colorectal pathologist.

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EUROANAESTHESIA 2025 CONGRESS REPORT
IZVEŠTAJ SA KONGRESA EUROANAESTHESIA 2025

Euroanaesthesia 2025, organized by the European Society of Anaesthesiology and Intensive Care (ESAIC), was held in Lisbon, Portugal, from 25 to 27 May 2025. The congress brought together several thousand participants from more than 100 countries, confirming its position as the leading European and one of the most influential global events in anaesthesiology, intensive care, and pain medicine.

Main Theme

The central theme of the congress was "Driving Innovation in Anaesthesiology, Intensive Care, and Pain Medicine". Particular emphasis was placed on: the implementation of digital technologies and artificial intelligence, sustainability in medical practice, patient-centred healthcare, and continuous improvement of safety and quality in perioperative care.

Scientific Programme

The congress opened with two highly anticipated keynote lectures:

Prof. Kate Leslie (Melbourne, Australia) addressed the transformation of anaesthesiology by 2050 and the role of emerging technologies in everyday practice.

Prof. Andre Dekker (Maastricht, The Netherlands) presented practical applications of artificial intelligence in personalized treatment and clinical decision-making.

Workshops and Interactive Sessions

Particular interest was attracted by: hands-on workshops on ultrasound techniques, regional anaesthesia, and haemodynamic monitoring, simulation laboratory sessions with realistic emergency scenarios and team-based training, and *Problem-Based Learning Discussions (PBLD)* and Serious Games, offering innovative, case-based educational formats.

Innovation Village and Industry Exhibition

For the second consecutive year, the Innovation Village showcased innovations in sustainability, technologies, and digital tools. The industry exhibition brought together leading companies presenting cutting-edge devices and software solutions for perioperative and intensive care medicine.

Key Topics and Highlight

Among the numerous sessions, several thematic areas were particularly prominent:

Airway management: advantages of video laryngoscopy over conventional techniques and the use of high-flow nasal oxygen (HFNO) during intubation.

Perfusion and tissue oxygenation monitoring: emerging technologies for microcirculatory assessment and therapeutic optimization.

Special populations: anaesthesia challenges in obese, oncological, and paediatric patients.

Neuroanaesthesia and neuroprotection: contemporary strategies in the management of traumatic brain injury.

Intensive care hot topics: sepsis management, multiorgan failure, and innovations in critical care.

Artificial intelligence: personalised therapy, predictive risk models, and novel educational platforms.

Awards and Publications

Outstanding scientific work was recognised through the Best Abstract Prize Competition, with monetary awards presented for the winners. All accepted abstracts will be published as an electronic supplement of the *European Journal of Anaesthesiology*, ensuring wide dissemination within the international scientific community.

Euroanaesthesia 2025 once again emphasized the importance of innovation, practical education, and multidisciplinary collaboration in advancing anaesthesiology and intensive care. The congress particularly highlighted the integration of cutting-edge technologies and novel educational models, which are expected to have direct impact on clinical practice and patient safety.

Postupak kada pacijent bez svesti nema dostupnog člana uže porodice za davanje pristanka

Ukoliko se pacijent bez svesti primi u zdravstvenu ustanovu a nije moguće doći do pacijentove uže porodice, zakonskog zastupnika ili lica za kontakt, a stanje pacijenta zahteva hitno sprovođenje terapijskih mera ili operativnog zahvata radi očuvanja života i sprečavanja pogoršanja teškog zdravstvenog stanja, postupa se na sledeći način:

Konzilijum lekara sa dežurnim lekarom (u zavisnosti od okolnosti) donosi odluku o neodložnom započinjanju medicinskih mera.

U medicinsku dokumentaciju se unosi beleška o sledećem:

Da je pacijent bez svesti i nije sposoban da dâ pristanak;

Da nije moguće dobiti pristanak od uže porodice ili zakonskog zastupnika;

Kratak opis medicinske indikacije i razloga za hitnost;

Vrsta planirane intervencije;

Imena i prezimena lekara koji su doneli odluku uz svojeručni potpis.

U belešci se navodi da je postupanje u skladu sa članom 15 Zakona o pravima pacijenta Republike Srbije.

Ukoliko se porodica kasnije identifikuje i uspostavi se kontakt sa njom, neophodno ih je informisati o preduzetim merama.

Napomena: U svim slučajevima neophodno je strogo dokumentovanje svih odluka i preduzetih mera radi zaštite pacijenta i zdravstvenih radnika.

Dr Milica Gojković

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a) Original Research Articles: These should present novel findings and include an abstract. The text should not exceed 3,500 words. While there is no formal limit on references, we recommend including no more than 50.

b) Review Articles: These should provide a comprehensive, balanced, and fully referenced analysis of existing literature. Review articles may be up to 8,000 words. Although there is no formal reference limit, we advise against exceeding 50 references.

c) Case Reports: These should describe conditions that offer new insights, highlight rare but modifiable disorders, or propose innovative treatments. Case reports should be no longer than 1,500 words, with up to 10 references.

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2. Manuscript Preparation

Manuscripts must be prepared in Microsoft Word using Times New Roman, 12-point font, with double-spacing and 2.54 cm margins on all sides. Page numbers should be positioned in the bottom-right corner.

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b) Abstract: Required for all submissions. For original research, the abstract must be structured into Introduction, Methods, Results, and Conclusion, and must not exceed 250 words. Both English and Serbian versions are required.

c) Keywords: Provide 3-6 relevant keywords. These may be adjusted to align with Medical Subject Headings (MeSH) standards.

d) Main text: The main text should be organized into the following sections: Introduction, Methods, Results, Discussion, and Conclusion, following the IMRAD structure.

e) References: Follow the Vancouver citation style https://en.wikipedia.org/wiki/Vancouver_system and https://www.ncbi.nlm.nih.gov/books/NBK7256/. Include DOIs for referenced articles where possible. References should be numbered consecutively as they appear in the text.

f) Tables and figures: These should either be included at the end of the manuscript or submitted as separate files. We recommend limiting tables and figures to six, with appropriate titles and legends, numbered in the order of their appearance in the text. Ensure figures are high-resolution (minimum 300 dpi). For previously published tables, graphs, diagrams or figures, provide the original source and written permission from the copyright holder. Please note that color attachments will be available online, while printed versions will be in black and white unless color printing is specifically requested by authors, which incurs additional costs.

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3. Ethical Considerations

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