Publishing Sector of the Society of Physicians of Vojvodina of the Medical Society of Serbia, Novi Sad, Vase Stajica 9
Copublisher: Faculty of Medicine Novi Sad

# MEDICAL REVIEW

**JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA**
***THE FIRST ISSUE WAS PUBLISHED IN 1948***



MEDICAL REVIEW is published bimonthly (six issues per year) with a circulation of 1.000 copies. The annual payment fee in 2025, for individuals from the territory of Serbia, is 4,000.00 dinars (the value-added tax included), 6,000.00 dinars for individuals from Serbia who are not members of the Society of Physicians of Vojvodina of the Medical Society of Serbia, 80 Euros for authors outside the territory of Serbia, and 9,000.00 dinars (+ VAT) for institutions. The payment account is: 340-1861-70 or 115-13858-06, "Annual subscription for Medical Review".



**The manuscripts are submitted at: aseestant.ceon.rs/index.php/medpreg/. Editorial Office Address: Društvo lekara Vojvodine Srpskog lekarskog društva, 21000 Novi Sad, Vase Stajića 9, Tel. 021/521-096; 063/81 33 875, E-mail: dlvsldnovisad@gmail.com; Website: www.dlv.org.rs**

Printed by: "Feljton" Novi Sad

Izdavačka delatnost Društva lekara Vojvodine Srpskog lekarskog društva, Novi Sad, Vase Stajića 9
Suizdavač: Medicinski fakultet Novi Sad

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**ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA**
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Štamparija: »Feljton« Novi Sad

M E D I C A L  R E V I E W
JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA
Novi Sad Vase Stajića 9 Serbia

Med Pregl 2025; LXXVIII (9-12): 219-324. Novi Sad: September-December.

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## *SADRŽAJ*

Med Pregl 2025; LXXVIII (9-12): 223-224. Novi Sad: septembar-decembar.

# LETTER FROM THE EDITOR
# *PISMO UREDNIKA*

*Dear Colleagues,*

In this issue of Medical Review, we are pleased to present a diverse collection of editorials, original studies, review articles, and case reports, while also taking the opportunity to reflect on the valuable contributions published in the previous issue.

The previous issue opens with an *editorial* by **Fogt**, who critically examines the phenomenon of diagnostic agreement within medical institutions. The author argues that apparent concordance among clinicians may sometimes reflect shared institutional interpretive culture rather than true diagnostic accuracy. By highlighting the roles of cognitive bias, group dynamics, and training environments, the article emphasizes the importance of cross-institutional collaboration and diversified diagnostic perspectives in order to improve diagnostic reliability in modern medicine [1]. In the second *editorial*, **Mobasheri** provides a concise update on the potential of cell and gene therapy for osteoarthritis, focusing on the therapeutic concept of TissueGene-C. The article discusses how engineered cells capable of expressing transforming growth factor-β1 may modulate synovial inflammation, promote cartilage repair, and alleviate pain through macrophage polarization and neurobiological mechanisms. This contribution outlines the promising future of regenerative approaches in the management of osteoarthritis [2].

Among the *original studies*, **Kitić et al**. analyze health-related quality of life in patients with chronic wounds using the Wound-QoL-17 instrument. Their findings highlight the profound multidimensional burden of chronic wounds on physical, psychological, and social well-being, emphasizing the importance of comprehensive patient-centered care in wound management [3]. In another clinical investigation, **Marinković et al**. examine predictors of outcome after carpal tunnel release surgery. The study identifies several clinical and demographic factors that may influence postoperative recovery and functional outcomes, providing useful insights for surgical decision-making and patient counseling [4]. The study by **Simeunović et al.** focuses on donor deferral in blood donation systems. By analyzing the reasons for donor rejection, the authors demonstrate how systematic evaluation of deferral patterns may improve recruitment strategies and contribute to a more sustainable and stable blood supply [5]. A further contribution by **Brusnjai et al.** explores the clinical characteristics and treatment outcomes of patients with severe exacerbations of chronic obstructive pulmonary disease. The results underline the clinical complexity and high morbidity associated with these episodes, highlighting the importance of timely recognition and optimized therapeutic strategies in managing severe COPD exacerbations [6]. In the field of rehabilitation medicine, **Đurić et al.** present a cross-sectional study exploring parental perspectives on robotic-assisted gait training for children with cerebral palsy. The authors report generally positive parental attitudes toward this advanced rehabilitation modality, emphasizing its potential role in improving mobility and functional independence in affected children [7]. The study by **Ristić et al.** investigates quality of life in patients with pacemakers. The results demonstrate that although pacemaker implantation significantly improves cardiac rhythm stability, patient-reported outcomes remain influenced by multiple psychosocial and clinical factors that should be addressed during long-term follow-up [8]. Another orthopedic-focused study by **Subašić et al.** examines quality of life after anterior cruciate ligament reconstruction with concomitant meniscal injury. The authors highlight the importance of comprehensive postoperative rehabilitation and individualized management in order to achieve optimal functional recovery and patient satisfaction [9].

The *review article* by **Aleksandrić et al.** discusses the prediction of outcomes after total knee arthroplasty based on psychophysical testing. By integrating physical and psychological evaluation tools, the authors propose a more holistic approach to preoperative patient assessment, which may improve outcome prediction and guide individualized treatment planning [10].

Several informative *case reports* further enrich this issue. **Dimitrić et al.** present testicular torsion as a rare complication following inguinal hernia repair, emphasizing the need for early recognition and prompt surgical intervention in order to prevent irreversible testicular damage [11]. A challenging dermatologic-oncologic case is described by **Đozić et al.**, who report squamous cell carcinoma arising in a patient with inherited epidermolysis bullosa. The authors discuss diagnostic and therapeutic dilemmas, particularly regarding the difficult decision of limb amputation in advanced disease [12]. **Isaković et al.** report a case of gallbladder perforation successfully managed conservatively. Their report contributes to the ongoing discussion about individualized treatment approaches in selected patients with this rare but serious complication [13]. Another rare condition is presented by **Šajinović et al.**, who describe a patient with eosinophilic granulomatosis with polyangiitis followed over a four-year period. This longitudinal observation provides valuable insights into disease progression and therapeutic response [14]. The case presented by **Tomić et al.** describes perineural metastasis of cutaneous squamous cell carcinoma involving the nasal and periocular region. The authors highlight the diagnostic challenges and the importance of early recognition of perineural spread in aggressive skin malignancies [15]. Finally, **Selaković et al.** discuss solitary rectal ulcer syndrome through a case report and literature review, focusing on common diagnostic and therapeutic pitfalls associated with this uncommon condition [16].

In the current issue, **McSwan and Mobasheri** present an insightful *editorial* addressing the evolving concept of self-healing in musculoskeletal pain management. The authors emphasize the importance of transitioning from passive, symptom-oriented care toward a multimodal, patient-centered approach that integrates biological, psychological, and behavioral mechanisms of recovery. By highlighting the role of self-efficacy, lifestyle interventions, and endogenous repair processes, this contribution outlines a forward-looking framework for improving long-term outcomes in patients with chronic musculoskeletal conditions [17].

Among the *original studies*, **Milankov and Pejaković** investigate the relationship between body mass index and anterior cruciate ligament pathology. Their work integrates mechanical and inflammatory mechanisms, demonstrating how excess adiposity contributes not only to increased biomechanical stress but also to systemic inflammation, ultimately affecting ligament integrity and postoperative recovery [18]. **Batinica Pamuk et al.** analyze chronic health risks associated with nitrate and nitrite exposure in unpurified chlorinated drinking water in the Autonomous Province of Vojvodina. Their findings raise important public health concerns regarding environmental exposure and underline the need for improved water quality monitoring and preventive strategies [19]. **Stanković et al.** focus on early neurological recovery following anterior cervical discectomy with cage fusion. The study highlights key clinical factors influencing postoperative outcomes and supports the effectiveness of this surgical approach in selected patients [20]. **Petrić et al.** evaluate the efficacy of molnupiravir in the treatment of COVID-19 infection. Their results contribute to the growing body of evidence on antiviral therapy and its role in reducing disease severity and improving clinical outcomes [21]. **Petrović et al.** investigate the efficacy of preoperative pregabalin in acute post-thoracotomy pain, demonstrating that perioperative administration with an additional postoperative dose provides superior analgesia during the first postoperative day without increasing opioid consumption or sedation, thereby underscoring the importance of dosing timing in optimising postoperative pain management [22].

The *review articles* further enrich this issue. **Pejin et al.** provide a comprehensive overview of minimally invasive and non-invasive treatment options for benign thyroid nodules, emphasizing patient selection and procedural safety [22]. **Šajinović et al.** discuss eosinophilic granulomatosis with polyangiitis, offering a detailed synthesis of current knowledge on pathogenesis, diagnosis, and management [23]. **Garipi et al.** explore the role of flexibility and joint mobility in injury prevention, highlighting their significance in both athletic and

general populations [24]. **Uram Benka et al.** present important considerations in anesthesia for children with anterior mediastinal masses, proposing an algorithm for safer perioperative management [25].

In the section of *professional articles*, **Rodić J et al.** address ethical and evidence-based management of neurosurgical emergencies in pregnancy, emphasizing the complexity of decision-making when maternal and fetal outcomes must be balanced [26].

Several *case reports* illustrate rare and challenging clinical scenarios. **Kotur et al.** describe an isolated orbital relapse of follicular lymphoma detected by PET/CT, highlighting the diagnostic value of advanced imaging techniques [27]. **Dolamić et al.** present paradoxical sinus deceleration during dobutamine stress echocardiography, discussing its diagnostic and therapeutic implications [28]. **Tešić et al.** report a combined endoscopic neurosurgical procedure in the treatment of obstructive hydrocephalus, demonstrating the feasibility of addressing multiple targets in a single session [29]. **Rodić D et al.** describe the use of customized 3D-printed guides in cranial reconstruction, emphasizing the role of personalized medicine and surgical innovation [30]. Finally, **Azarić et al.** present a rare case of ruptured pontine cavernoma with favorable recovery, illustrating the importance of timely diagnosis and multidisciplinary care [31].

We hope that the studies presented in last two issues will contribute to better clinical understanding, encourage interdisciplinary collaboration, and stimulate further research across multiple fields of medicine.

With kind regards,

*Prof. dr Radmila Matijević*
*Editor-in-Chief*

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Med Pregl 2025; LXXVIII (9-12): 225-227. Novi Sad: septembar-decembar.

EDITORIAL
*UVODNIK*

# EMBRACING, ADOPTING AND EXPANDING THE SELF-HEALING CONCEPT TO ADVANCE MUSCULOSKELETAL PAIN MANAGEMENT

## *PRIHVATANJE, USVAJANJE I PROŠIRENJE KONCEPTA SAMOIZLEČENJA U CILJU UNAPREĐENJA LEČENJA BOLA MIŠIĆNO-SKELETNOG SISTEMA*

**Joyce MCSWAN[1] and Ali MOBASHERI [2–6]**

ORCID NUMBER
Joyce McSwan – 0009-0008-9127-1194
Ali Mobasheri – 0000-0001-6261-1286

PainWISE Pty Ltd, Gold Coast, Australia[1]
Research Unit of Health Sciences and Technology, Physics and Technology, University of Oulu, Oulu, Finland[2]
Department of Personalized Medicine,
State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania[3]
Department of Joint Surgery, Sun Yat-sen University, Guangzhou, China[4]
Faculté de Médecine, Université de Liège, Liège, Belgium[5]
Department for Health Sciences, Medicine and Research, Center for Regenerative Medicine,
Faculty of Health and Medicine, University for Continuing Education Krems, Krems, Austria[6]

Editorial
*Uvodnik*
UDK 616.7:615.85
https://doi.org/10.2298/MPNS2512225M

The rising global burden of painful musculoskeletal (MSK) conditions – particularly chronic conditions such as low back pain (LBP) and osteoarthritis (OA) – represents one of the most pressing public health challenges of our time [1–4]. Traditional primary clinical care models are largely centered on unimodal, passive interventions, pharmacological management (including polypharmacy and general overreliance on opioids), or surgical procedures [5]. Despite their widespread use, these approaches have consistently failed to curb the growing MSK pain epidemic, especially among older adults and geriatric populations [6]. This limited effectiveness is largely attributable to the narrow focus of traditional strategies, which often rely on single-modality treatments with modest long-term benefits and substantial risks of adverse effects [7].

The escalating prevalence and chronicity of MSK pain underscores the need for a paradigm shift toward multimodal pain management - an integrated, evidence-based approach that combines pharmacological and non-pharmacological therapies tailored to individual patient needs. The persistent inability to deliver cost-effective and sustainable MSK pain care highlights the shortcomings of models rooted in passive patient dependence and symptom suppression. Instead, there is a growing recognition of the need to harnesses patients' intrinsic biological and psychological capacities for recovery.

Within this evolving context, the concept of **self-healing** has emerged as a critical and integrative framework for contemporary MSK pain management [8,9]. Self-healing extends beyond traditional notions of self-care [10] and self-efficacy [11,12]. It represents a patient-centered, multimodal paradigm that purposefully integrates self-care, self-management, and self-efficacy with the body's innate physiological restorative mechanisms [8]. Importantly, self-healing is not merely a behavioral strategy; rather, it constitutes a multidisciplinary framework grounded on biological and physiological processes that support tissue repair and pain modulation.

Central to the self-healing concept is recognition of the body's inherent ability to transform from a pro-inflammatory state toward a pro-resolving and reparative milieu, thereby promoting tissue homeostasis and positively influencing pain perception and coping capacity. By emphasizing these endogenous mechanisms, the self-healing framework empowers individuals to become active participants in their recovery [13].

From a mechanistic standpoint, the effectiveness of self-healing is underpinned by the close interconnection between psychological and physiological systems. Self-efficacy – defined as a patient's belief in their capacity to influence health outcomes – plays a pivotal role in modulating neurobiological pain pathways. This influence extends beyond contextual effects, contributing to enhanced placebo responses and attenua-

✉ Corresponding author: Ali Mobasheri, E-mail: ali.mobasheri@oulu.fi

***Abbreviations***

| | |
|---|---|
| MSK | – musculoskeletal |
| LBP | – low back pain |
| OA | – osteoarthritis |

tion of nocebo effects [14,15]. Moreover, self-healing emphasizes regulation of key physiological systems, particularly the autonomic nervous system [8]. Interventions such as structured physical activity, optimized sleep, and targeted nutritional strategies can enhance parasympathetic tone, reduce systemic anti-inflammation, and improved overall pain resilience [16]. Together, these approaches offer a coherent, evidence-based pathway for activating intrinsic repair mechanisms.

Adopting the self-healing paradigm necessitates a fundamental shift in clinical practice, particularly within primary care settings [7]. Clinicians must move beyond a focus on symptom suppression toward a facilitative role that emphasizes education and skill development, enabling patients to cultivate their own healing capacities. This transition requires clinicians to be equipped with tools that extend beyond conventional treatment guidelines, including strategies for behavioral activation, cognitive reframing, and targeted lifestyle modification. Such competencies are especially relevant for managing persistent conditions such as LBP and OA in domestic and occupational contexts [17,18]. In this regard, the self-healing model provides a robust structural framework for integrating evidence-based interventions in conditions that typically demonstrate poor outcomes under passive care.

In conclusion, the increasing chronicity of MSK pain demands bold, holistic solutions. The self-healing concept represents the logical and necessary evolution of self-management, integrating advances in clinical science with patient empowerment [8]. By formally embedding self-healing principles into clinical guidelines, professional education, and primary care practice, the medical community can more effectively address the global MSK pain crisis, enhance patient autonomy, and promote a more sustainable and effective system for long-term MSK pain management and improved MSK health outcomes [19–22].

Funding: A. M. wishes to acknowledge the financial support of the Research Council of Lithuania (Lietuvos Mokslo Taryba) under the Attracting Foreign Researchers for Research Implementation Program (Grant No. 01.2.2-LMT-K-718-02-0022), Research Council of Finland/Suomen Akatemia Profi 6, grant numbers 336449 and 351568, awarded to the University of Oulu. A.M. also acknowledges funding from Horizon Europe (PROTO-Advanced PeRsOnalized Therapies for Osteoarthritis-TACKLING INFLAMMATION TO IMPROVE PATIENT OUTCOMES, grant agreement ID 101095635, https://cordis.europa.eu/project/id/101095635 and ENgineered CArtilage from Nose for the Treatment of Osteoarthritis (ENCANTO), grant agreement ID 101137315, https://cordis.europa.eu/project/id/101137315). A.M. also acknowledges research networking support from the European Cooperation in Science and Technology COST Association Action CA21110—Building an Open European Network on Osteoarthritis Research (NetwOArk); https://www.cost.eu/actions/CA21110/.

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Rad je primljen 3. XII 2025.
Recenziran 3. XII 2025.
Prihvaćen za štampu 3. XII 2025.
BIBLID.0025-8105:(2025):LXXVIII:9-12:225-227.

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Med Pregl 2025; LXXVIII (9-12): 229-234. Novi Sad: septembar-decembar.

ORIGINAL STUDIES
*ORIGINALNI NAUČNI RADOVI*

# BODY MASS INDEX AND THE ANTERIOR CRUCIATE LIGAMENT – INTEGRATING MECHANICAL AND INFLAMMATORY MECHANISMS

# *INDEKS TELESNE MASE I PREDNJI UKRŠTENI LIGAMENT – SPOJ MEHANIČKIH I INFLAMATORNIH MEHANIZAMA*

**Andrijana MILANKOV[1,2] and Slađana PEJAKOVIĆ[1,2]**

ORCID NUMBER
Andrijana Milankov – 0000-0001-5815-3892
Slađana Pejaković – 0000-0002-9654-6395

University Clinical Center of Vojvodina, Novi Sad
Clinic for Endocrinology, Diabetes and Metabolic Disorders[1]
University of Novi Sad, Faculty of Medicine Novi Sad
Department of Internal Medicine[2]

Original study
*Originalni naučni rad*
UDK 613.25:616-008.6]-06:616.728.3
https://doi.org/10.2298/MPNS2512229M

**Abstract**

**Introduction.** Obesity is a chronic metabolic disorder characterised by excess adiposity, persistent low-grade inflammation, and high frequency of musculoskeletal complications in both athletic and non-athletic populations. Body mass index and fat distribution, particularly visceral adiposity, are key determinants of metabolic and orthopaedic risk, including disorders of the knee tendons and ligaments. **From adiposity to ligament pathology.** In obesity, white adipose tissue undergoes phenotypic remodelling toward a pro-inflammatory state, marked by immune cell infiltration, increased secretion of cytokines and adipokines, and reduced adiponectin levels. These alternations promote lipotoxicity and ectopic fat deposition in skeletal muscle, ligaments, fat pads, and entheses, contributing to sarcopenic obesity, angiofibroblastic degeneration, and impaired ligament healing. **Clinical implications.** Elevated body mass index increases mechanical loading and alters lower-limb biomechanics, thereby promoting repetitive microtrauma, chronic inflammation, and higher incidence of tendinopathies, particularly of the extensor mechanism and pes anserinus. In individuals with body mass index above 25 kg/m², published studies report a higher prevalence of multiligament knee injuries, a greater proportion of trauma-related anterior cruciate ligament ruptures, increased postoperative complications, and delayed functional recovery. However, heterogeneity in study design limits precise quantification of effect sizes. **Conclusion.** Excess adiposity likely increases anterior cruciate ligament injury risk through the combined effects of mechanical overload and obesity-related inflammation and is associated with more extensive ligament damage and a less favourable postoperative course. Integrated interventions targeting fat-mass reduction, metabolic optimisation, and neuromuscular conditioning may enhance recovery, reduce re-injury risk, and support long-term knee joint health. This conceptual framework is applicable across age groups in both recreational and competitive sports populations.

**Key words:** Anterior Cruciate Ligament Injuries; Body Mass Index; Obesity; Adiposity; Inflammation; Sarcopenia; Metabolic Syndrome; Risk Factors

**Sažetak**

**Uvod.** Gojaznost je hronična metabolička bolest praćena porastom masne mase, perzistentnom niskogradusnom inflamacijom i čestim mišićno-koštanim komplikacijama kod sportista i opšte populacije. Indeks telesne mase i raspored masnog tkiva, naročito visceralna adipoznost, ključni su determinanti metaboličkog i ortopedskog rizika, uključujući patologiju tetiva i ligamenata kolena**. Od adipoznosti do patologije ligamenata.** U gojaznosti belo masno tkivo prelazi u proinflamatorni fenotip sa infiltracijom imunskih ćelija i pojačanom sekrecijom citokina i adipokina uz snižene nivoe adiponektina. Lipotoksičnost i ektopično deponovanje masti u skeletnim mišićima, ligamentima, masnim jastučićima i na entezama doprinose sarkopeničnoj gojaznosti, angiofibroblastičnoj degeneraciji i oslabljenoj reparaciji ligamenta. **Kliničke implikacije.** Povišen indeks telesne mase povećava mehaničko opterećenje i menja biomehaniku donjih ekstremiteta, što pogoduje ponavljanim mikrotraumama, hroničnoj inflamaciji i učestalijim tendinopatijama ekstenzornog mehanizma i *pes anserinus* sindromu. Kod osoba sa indeksom telesne mase iznad 25 kg/m², studije opisuju češće višeligamentne povrede kolena, veći udeo traumatskih ruptura prednjeg ukrštenog ligamenta, više postoperativnih komplikacija i sporiji funkcionalni oporavak, ali heterogenost dizajna ograničava preciznu procenu efekta. **Zaključak.** Gojaznost verovatno povećava rizik od povrede prednjeg ukrštenog ligamenta kombinacijom mehaničkih i inflamatornih mehanizama i povezana je sa težim obrascem povrede i nepovoljnijim postoperativnim tokom. Integrisane strategije koje kombinuju redukciju masne mase, metaboličku optimizaciju i neuromišićni trening mogu unaprediti oporavak, smanjiti rizik ponovne rupture i očuvati dugoročno zdravlje kolena. U planiranju lečenja i povratka sportu potrebno je uključiti savetovanje o ishrani i nadzor komorbiditeta tokom čitavog postoperativnog perioda.

**Ključne reči:** povrede prednjeg ukrštenog ligamenta; indeks telesne mase; gojaznost; masnoća; inflamacija; sarkopenija; metabolički sindrom; faktori rizika

✉ Corresponding author: Andrijana Milankov, E-mail: andrijana.milankov@mf.uns.ac.rs

***Abbreviations***

ACL – anterior cruciate ligament
ADP – air-displacement plethysmography
BIA – bioelectrical impedance analysis
bFGF – basic fibroblast growth factor
BMI – body mass index
COX-1 – cyclooxygenase 1
COX-2 – cyclooxygenase 2
CT – computed tomography
DXA – dual-energy X-ray absorptiometry
EASO – European Association for the Study of Obesity
ESPEN – European Society for Clinical Nutrition and Metabolism
EWGSOP2 – European Working Group on Sarcopenia in Older People 2
FFA/FFAs – free fatty acid(s)
IgG – immunoglobulin G
IL-1β – interleukin 1 beta
IL-1Ra – interleukin 1 receptor antagonist
IL-4 – interleukin 4
IL-6 – interleukin 6
IL-8 – interleukin 8
IL-10 – interleukin 10
IL-13 – interleukin 13
IL-17 – interleukin 17
IL-21R – interleukin 21 receptor
IL-33 – interleukin 33
M1 – classically activated (pro-inflammatory) macrophage phenotype
MRI – magnetic resonance imaging
NK – natural killer (cells)
PCOS – polycystic ovary syndrome
SARC-F – Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls
SPPB – Short Physical Performance Battery
TGF-β – transforming growth factor beta
Th17 – T helper 17
TNF-α – tumor necrosis factor alpha
TUG – Timed Up and Go
WAT – white adipose tissue
WHR – waist-hip ratio

## Introduction

Obesity has long been recognized as a major public health problem with a high incidence and prevalence worldwide. As early as the time of Hippocrates, it was observed that individuals with excessive body weight experienced sudden death more frequently, highlighting the long-standing medical awareness of obesity-related risk. The conceptual understanding of obesity has evolved substantially over time, with the most significant advances occurring during the second half of the 20th century and the beginning of the 21st century. During this period, obesity-associated disorders were systematically identified, the critical role of fat distribution in the development of complications was established, key pathophysiological mechanisms were elucidated, diagnostic criteria were standardized, and increasingly precise methods for assessing body fat mass were developed. According to the World Health Organization, the fundamental parameter for defining nutritional status and diagnosing obesity is body mass index (BMI). Based on BMI (kg/m²) values, individuals are classified as underweight (BMI < 18.5), normal weight (18.5-24.9), overweight or pre-obesity (25.0-29.9), and obese (≥30). Obesity is further stratified into class I (30.0-34.9), class II (35.0-39.9), and class III (≥ 40). However, because total body mass does not necessarily reflect body fat content or distribution, more accurate assessment of obesity requires direct measurement of fat mass. Available methods include bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), hydrostatic weighing, air-displacement plethysmography (ADP), three-dimensional body scanning, and skinfold thickness measurement using calipers [1].

With respect to fat distribution – which largely determines the risk and type of obesity-related complications – obesity is commonly categorized as abdominal (central, visceral) or peripheral. Waist circumference and waist-hip ratio (WHR) are widely used for rapid characterization of obesity type.

Currently, obesity is defined as a chronic metabolic disease characterized by excessive accumulation of adipose tissue. Despite advances in diagnostic approaches and therapeutic strategies, obesity continues to present growing challenges, as it is associated with a wide spectrum of metabolic, cardiovascular, reproductive, psychological, and musculoskeletal disorders that significantly impair quality of life and increase overall mortality. Excess adipose tissue, particularly visceral fat, induces a state of chronic low-grade inflammation and is considered a central driver of obesity-related complications, including insulin resistance, type 2 diabetes mellitus, arterial hypertension, cardiovascular disease, dyslipidemia, gastrointestinal and urogenital disorders, polycystic ovary syndrome (PCOS), infertility, depression, malignancy, and musculoskeletal disorders [2–4].

### From adiposity to ligament pathology: plausible biological pathways

White adipose tissue (WAT) functions not only as a lipid storage depot but also as an endocrine organ and immunological organ. It consists of mature adipocytes, preadipocytes, adipocyte precursors, and a diverse population of immune cells. WAT secretes more than 50 hormones and signaling molecules – collectively termed adipokines – that regulate metabolism and proper immune function. In individuals of normal body weight, adipose tissue synthesizes anti-inflammatory adipokines, including interleukin (IL)-4, IL-10,

IL-13, IL-1 receptor antagonist (IL-1Ra), transforming growth factor-beta (TGF-β), adiponectin, and apelin. In contrast, obesity is characterized by a shift toward a pro-inflammatory adipokine profile, with increased secretion of IL-1β, IL-6, TNF-α, resistin, visfatin, leptin, angiotensin II, and plasminogen activator inhibitor-1. This pro-inflammatory secretion pattern arises largely from immune–cell infiltration in adipose tissue, particularly macrophages, which accumulate in WAT and undergo polarization toward a pro-inflammatory M1-like phenotype. In addition to macrophages, adipose tissue contains B cells, T cells, dendritic cells, and neutrophils, all of which contribute to immune modulation. In obesity, B cells infiltrate WAT, secrete pro-inflammatory cytokines, and produce autoreactive IgG antibodies that amplify local inflammation and promote Th17 responses. Through antigen presentation, B cells also activate T cells, which in turn activate dendritic cells and macrophages, reinforcing the inflammatory cascade [5].

Beyond localized adipose tissue inflammation, excessive fat mass promotes a state of systemic chronic low-grade inflammation that underlines the development of obesity-related comorbidities. Increasing attention has recently been directed toward the musculoskeletal consequences of obesity. Conditions such as sarcopenic obesity, osteoporosis, osteoarthritis, and ligament disorders are increasingly recognized as integral components of metabolic syndrome and are closely linked to the chronic inflammatory milieu characteristic of obesity.

**Clinical implications**

Sarcopenia is defined as a loss of skeletal muscle mass, muscle quality, and strength. Although it most commonly develops with aging – at a rate of approximately 0.5-1% per year – it may also arise secondary to neurological disorders, mitochondrial dysfunction, hormonal imbalance, adverse lifestyle factors, and chronic low-grade inflammation. Clinically, the European Working Group on Sarcopenia in Older People (EWGSOP2) recommends a stepwise approach in which low muscle strength represents the primary criterion ("probable sarcopenia"), reduced muscle quantity or quality confirms the diagnosis, and impaired physical performance denotes severe sarcopenia. Case identification may be supported by screening instruments such as the SARC-F questionnaire, followed by objective assessment of muscle strength (e.g., handgrip strength or five-times chair stand test), evaluation of muscle quantity or quality using body-composition technique (dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) in clinical practice), and measurement of physical performance using the tools such as gait speed, SPPB, TUG test, or the 400-m walk test.

When excess adiposity coexists with impaired muscle mass or function, sarcopenic obesity should be recognized as a distinct and clinically relevant entity. The ESPEN/EASO consensus defines sarcopenic obesity as the simultaneous presence of increased adiposity and reduced muscle mass and/or function and emphasizes a structured diagnostic approach based on validated, qualitative measures of both adiposity and muscle impairment, rather than reliance on a single fixed combination of historical cut-off values [6–9].

Skeletal muscle tissue exhibits high plasticity and continuous remodeling, rendering it particularly vulnerable to chronic low-grade inflammation. In the context of obesity, ectopic lipid deposition within non-adipose tissues – including skeletal muscle – leads to lipotoxicity, myosteatosis, and sarcopenic obesity **(Figure 1)** [3].

These functional alterations – characterized by compromised muscle integrity and persistent atrophy – are recognized risk factors for a range of musculoskeletal disorders, including tendinopathies, osteoporosis, osteoarthritis, and reduced preservation of range of motion in affected body segments, particularly the lower extremities [3].

A strong association has between described between sarcopenic obesity and metabolic syndrome. Because sarcopenic obesity is accompanied by disability, reduced physical activity, altered mechanical loading, and disrupted muscle biology due to lipid infiltration and lipotoxicity, together with chronic low-grade inflammation, it is likely to play a central role in the development of other musculoskeletal diseases [3,10].

Ligament disorders – including pain, inflammation, rupture, and impaired recovery following injury – have increasingly been linked to excess visceral adiposity and have become an important focus of investigation in both athletic and non-athletic populations. The mechanisms connecting adiposity to ligament pathology appear to be both mechanical and systemic in nature [10,11].

Mechanical mechanisms involve increased ligament loading and repetitive mechanical stress, particularly in the lower extremities, resulting from elevated BMI. Chronic overload promotes ligament inflammation, thereby predisposing to rupture. However, similar pathological ligament changes have also been observed in the upper extremities in individuals with obesity, suggesting that systemic inflammation plays a crucial etiological role [10,11].

The systemic effects of obesity on ligament health may be both direct and indirect [12]. Direct effects

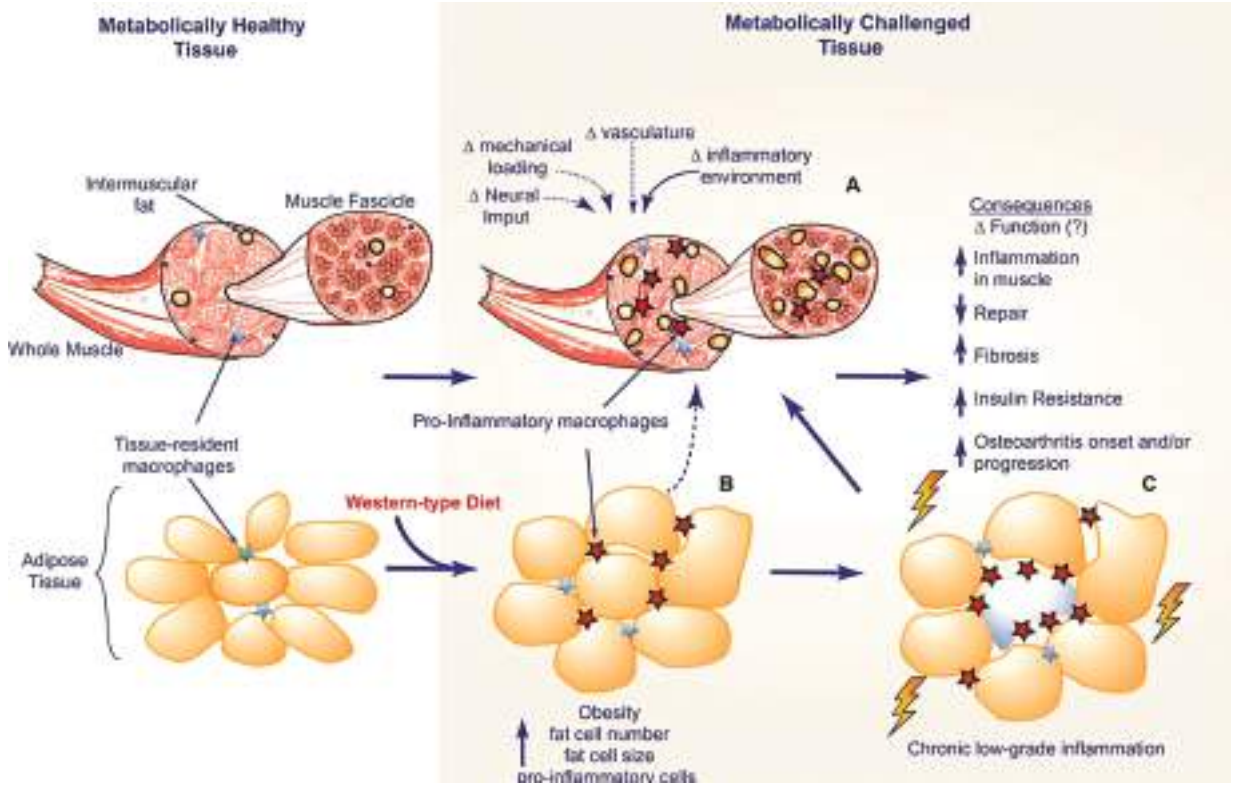


**Figure 1.** Structural and inflammatory alterations in muscle; (A) Factors compromising muscle structural integrity; (B) obesity-related changes in adipose tissue; (C) musculoskeletal consequences of chronic low-grade inflammation [3].

are mediated by bioactive peptides secreted by adipose tissue, while indirect effects arise from metabolic disturbances that negatively influence ligament structure [10,11]. Ligamentopathy was historically regarded as a degenerative, non-inflammatory condition. However, contemporary histopathological studies have demonstrated the presence of inflammatory cells and molecular markers within diseased ligament tissue, with earlier conclusions largely attributable to methodological limitations [13,14].

Histological analyses of chronically inflamed ligaments reveal an absence of acute inflammation; instead, tissue damage reflects failed cellular repair process associated with angiofibroblastic degeneration. Immune cells – including macrophages, mast cells, natural killer (NK) cells, and T cells – have been consistently identified in ligament biopsy specimens. Moreover, a broad spectrum of inflammatory cytokines has been detected, including IL-1β, IL-6, IL-8, IL-10, IL-17, IL-21 receptor, IL-33, COX-1, COX-2, TGF-β, TNF-α, and bFGF. In obesity, the balance between pro- and anti-inflammatory adipokines is markedly disrupted, resulting in sustained low-grade inflammation. Many of the cytokines overexpressed in obesity are also abundantly present in tendinopathies, providing a biological link between these conditions. Inflammatory cytokines (IL-6, IL-1β, TNF-α) are thought to drive the initiation and progression of chronic tendon inflammation by promoting cell proliferation, angiogenesis, extracellular matrix degeneration, tissue metaplasia, and secretion of pain mediators.

Hyperleptinemia and leptin resistance, characteristic features in obesity, have been associated with tenocyte degeneration, vascular proliferation, rupture at the tendon-bone interface, ectopic ossification following injury, and impaired healing. Reduced ligament healing capacity and a higher prevalence of chronic injury due to repetitive microtrauma in individuals with obesity have also been linked to decreased adiponectin levels and increased synthesis of free fatty acids (FFAs). FFAs exert lipotoxic effects through oxygen stress, lipid peroxidation, mitochondrial dysfunction, and induction of inflammatory cytokines. Although a direct causal relationship between FFAs and ligament disease has not been conclusively established, their lipotoxic effects have been documented in cartilage injury and osteoarthritis development [15–20].

Beyond intramuscular lipid accumulation, obesity is associated with increased fat deposition within ligaments themselves, as well as in the infrapatellar fat pad and at entheses – the sites of tendon and ligament insertion. These local fat depots are capable of producing inflammatory cytokines, thereby amplifying local inflammatory responses. Larger fat pads

correlate with higher cytokine production and may contribute to inflammation, pain, and rupture. Repetitive stress imposed on these fat pads by elevated BMI further promotes chronic low-grade inflammation, predisposing ligaments and tendons to inflammation. Collectively, the metabolic consequences of systemic obesity extend to local fat depots in adjacent muscles, ligament-bone insertions, adjacent fat pads, and even within ligament and tendon tissue itself, fostering inflammation, pain, and degeneration, and contributing to the development and progression of tissue damage [21–23].

Beyond inflammation, other obesity-associated comorbidities contribute to musculoskeletal pathology.

Elevated arterial blood pressure – commonly present in metabolic syndrome - induces local inflammation in tissue damage through vasoconstriction and impaired tissue perfusion. Dyslipidemia, including elevated cholesterol and triglyceride levels, has been directly linked to tendon and ligament pain and inflammation. Subendothelial lipoprotein deposition stimulates chemokine production and macrophage activation, leading to endothelial dysfunction and sustained inflammation [24, 25].

Increased BMI is also associated with reduced physical activity, while musculoskeletal disorders further limit exercise capacity, creating a self-perpetuating cycle of weight gain, mechanical overload, and inflammation. This cycle disproportionately affects the lower extremities and exacerbates tendon and ligament pathology.

Evidence indicates that a BMI >25 kg/m² (pre-obesity) is associated with reduced physical activity, increased comorbidity burden, and higher all-cause mortality [26,27]. Knee pathology, particularly osteoarthritis, is especially prevalent in individuals with obesity [28]. Knee tendinopathies may involve extensor mechanism – affecting quadriceps and patellar tendons – or the pes anserinus complex. Pes anserinus tendinopathy is common among obese women with valgus knee alignment and is characterized by pain during weight bearing activities, when standing, walking, or climbing stairs – at the insertion of the semimembranosus, semitendinosus, gracilis, and sartorius on the superomedial surface of the tibia. In these patients, repetitive friction of the hamstring tendons against the medial femoral condyle, often accompanied by inflammation of the anserine bursa, which is located between the tendon insertions and the posterior surface of the tibia, contributes to anserine bursitis as part of the tendinopathy complex [29,30].

Although clinical data on the relationship between elevated BMI and knee ligament pathology remain limited, available evidence suggests that individuals with obesity may be at increased risk of injury due to greater mechanical loading [30]. Rupture of the anterior cruciate ligament (ACL) is among the most common orthopedic injuries and is associated with reduced quality of life. While multiple modifiable and non-modifiable risk factors may contribute to ACL injury, increased BMI represents an important modifiable factor and has been associated with as many as 75% of non-contact ACL ruptures [27].

Existing studies report inconsistent findings regarding the association between BMI and ACL injury risk. However, higher BMI (pre-obesity and obesity) has been linked greater frequency of non-isolated (combined) ligament injuries, and, in some reports, higher re-rupture rates. Although obesity is more prevalent among women, ACL ruptures occur more frequently in men [4]. Other studies have reported a higher incidence of ACL injury in non-athletes and elevated BMI compared with athletes, with no clear association between BMI and re-rupture risk [31,32].

Regarding injury mechanism, no major differences have been observed between individuals with normal BMI and those with BMI >25 kg/m² in terms of contact versus non-contact injuries. However, a higher proportion of trauma-related injuries has been reported among pre-obese and obese individuals [27]. Chronic low-grade inflammation, metabolic dysregulation, increased mechanical loading, and reduced pre- and post-injury physical activity collectively contribute to impaired recovery, higher postoperative complications rates, and delayed functional restoration in this population [30,32].

Lifestyle modification – both dietary change and promotion of physical activity – is paramount for preventing complications of the musculoskeletal system [33]. Reducing body-fat mass significantly lowers the level of systemic chronic inflammation and mechanical loading, while increasing physical activity, all of which help prevent chronic disease.

## Conclusion

Elevated body mass index appears to increase anterior cruciate ligament injury risk through the combined effects of mechanical overload and systemic inflammation and is associated with a greater burden of multi-ligament injury, a higher proportion of trauma-related mechanisms, and increased postoperative complication rates. Given that body mass index is a modifiable risk factor, integrated strategies combining neuromuscular training, weight reduction, and metabolic optimization represent a rational approach to reducing injury risk and improving outcomes through the anterior cruciate ligament care pathway.

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Rad je primljen 24. XI 2025.
Recenziran 12. I 2026.
Prihvaćen za štampu 12. I 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:229-234.

Med Pregl 2025; LXXVIII (9-12): 235-242. Novi Sad: septembar-decembar.

# CHRONIC HEALTH RISKS ASSOCIATED WITH NITRATE AND NITRITE IN UNPURIFIED CHLORINATED DRINKING WATER IN THE AUTONOMOUS PROVINCE OF VOJVODINA

## *POVEZANI HRONIČNI ZDRAVSTVENI RIZICI ZBOG PRISUSTVA NITRATA I NITRITA U NEPREČIŠĆENOJ HLORISANOJ PIJAĆOJ VODI AUTONOMNE POKRAJINE VOJVODINE*

**Dragana BATINICA PAMUK[1], Emil ŽIVADINOVIĆ[2], Nataša DRAGIĆ[2,3] and Sanja BIJELOVIĆ[2,3]**

ORCID NUMBER
Dragana Batinica Pamuk – 0009-0002-7846-7236
Emil Živadinović – 0009-0008-0485-5045
Nataša Dragić – 0000-0001-8890-321X
Sanja Bijelović – 0000-0003-2142-7137

Public Health Institute of Subotica, Subotica[1]
Institute of Public Health of Vojvodina, Novi Sad[2]
University of Novi Sad, Faculty of Medicine Novi Sad[3]

Original study
*Originalni naučni rad*
UDK 614.777:628.1.033(497.113)
UDK 546.173/.175:543.544
https://doi.org/10.2298/MPNS2512235B

**Abstract**

**Introduction.** This study aimed to analyse nitrate and nitrite concentrations in unpurified chlorinated drinking water across the Autonomous Province of Vojvodina and to assess the associated chronic health risks for both adult and paediatric populations. **Material and Methods**. A retrospective analysis was performed using data from 2023 obtained from seven authorized, certified, and accredited public health institutions. A total of 11,919 samples of unpurified chlorinated drinking water were analysed. Nitrate and nitrite concentrations were determined using a spectrophotometric analytical method. Valued below the analytical detection limit were imputed as one-half of the respective detection limits. Health risk assessment was conducted by calculating the Hazard Quotient for adults and children in accordance with the United States Environmental Protection Agency methodology. **Results**. Elevated nitrite concentrations were identified in 456 samples (3.83%), with a mean concentration of 0.030 mg/L and a maximum value of 1.005 mg/L (national limit: 0.03 mg/L). Elevated nitrate concentrations were detected in 129 samples (1.08%), with a mean concentration of 5.229 mg/L and a maximum concentration of 139 mg/L (national limit: 50 mg/L). A Hazard Quotient value below one indicates the absence of non-carcinogenic health risk. For the average nitrate concentration, Hazard Quotient values were within acceptable limits for both adults (8.46E-02) and children (3.49E-01); however, Hazard Quotient values calculated using maximum nitrate concentrations exceeded the safety threshold (2.25E+00 for adults and 9.27E+00 for children). In contrast, Hazard Quotient for nitrites remained well below one for both average and maximum concentrations in both population groups. **Conclusion.** While average nitrate and nitrite concentrations in chlorinated drinking water do not pose a chronic health risk, elevated maximum nitrate concentrations represent a potential long-term health concern, particularly for children.

**Key words:** Nitrates; Nitrites; Drinking Water; Water Pollution; Halogenation; Water Quality; Risk Assessment; Public Health; Environmental Medicine

**Sažetak**

**Uvod**. Studija ima za cilj analizu koncentracija nitrata i nitrita u neprečišćenoj hlorisanoj vodi za piće na teritoriji Autonomne Pokrajine Vojvodine i procenu povezanih zdravstvenih rizika za decu i odrasle. **Materijal i metode.** Sprovedena je retrospektivna analiza podataka iz 2023. godine, prikupljenih iz sedam ovlašćenih, sertifikovanih i akreditovanih Zavoda za javno zdravlje. Istraživanje je obuhvatilo 11.919 uzoraka neprečišćene hlorisane pijaće vode. Koncentracije nitrata i nitrita određene su spektrofotometrijskom analitičkom tehnikom. Vrednosti ispod granice detekcije modelovane su kao polovina laboratorijske granice detekcije. Hazardov koeficijent za odrasle i decu izračunat je primenom metodologije Agencije za zaštitu životne sredine Sjedinjenih Američkih Država. **Rezultati.** Povišene koncentracije nitrita pronađene su u 456 uzoraka (3,83%), sa prosekom od 0,030 mg/L i maksimumom od 1,005 mg/L (nacionalna vrednost: 0,03 mg/L). Povišeni nivoi nitrata zabeleženi su u 129 uzoraka (1,08%), sa prosekom od 5,229 mg/L i maksimumom od 139 mg/L (nacionalna vrednost: 50 mg/L). Koeficijent opasnosti ispod jedan ukazuje na odsustvo rizika od nekancerogenih efekata. Za prosečne koncentracije nitrata, koeficijent opasnosti bio je prihvatljiv (8,46E – 02 za odrasle i 3,49E – 01 za decu), dok za maksimalne koncentracije nije bio prihvatljiv (2,25E + 00 za odrasle i 9,27E + 00 za decu). Za nitrite, koeficijent opasnosti bio je znatno ispod jedan, što je prihvatljivo za prosečne i maksimalne koncentracije i za odrasle i za decu. **Zaključak.** Prosečne koncentracije nitrata i nitrita ne predstavljaju zdravstveni rizik; međutim, maksimalne koncentracije nitrata mogu predstavljati potencijalni hronični zdravstveni rizik, naročito za decu.

**Ključne reči:** nitrati; nitriti; voda za piće; zagađenje vode; hlorinacija; kvalitet vode; procena rizika; javno zdravlje; medicina životne sredine

## Introduction

Safe and sufficient drinking water is fundamental to public health and overall well-being [1], as emphasized by global initiatives such as the 2015 United Nations Sustainable Development Goals [1,2]. Water is indispensable for human survival and it must comply with strict safety standards to ensure freedom from microbial, physical, and chemical contamination [3]. Among chemical contaminants, nitrate is one of the

✉ Corresponding author: Dragana Batinica Pamuk, E-mail: dragana.batinica2014@gmail.com, natasa.dragic@mf.uns.ac.rs

***Abbreviations***

EPA – Environmental Protection Agency
EU – European Union
HQ – Hazard Quotient
ISO – International Organization for Standardization
NPCW – Unpurified Chlorinated Drinking Water
SRPS – Serbian Standards
WHO – World Health Organization
APV – Autonomous Province of Vojvodina

most prevalent in groundwater, second only to pesticides. Other nitrogenous compounds – including nitrite, ammonia, and organic nitrogen – are likewise critical indicators of water quality and are closely monitored worldwide [4]. The nitrate cycle illustrates the generation and transformation of nitrogen compounds through both natural processes and anthropogenic activities. Atmospheric nitrogen is initially converted into plant-available forms by soil microorganisms. Through ammonification, organic nitrogen is transformed into ammonia, which is subsequently oxidized during nitrification to produce nitrite and nitrate. These compounds may infiltrate groundwater or be assimilated by plants and microorganisms, eventually returning to the atmosphere as nitrogen gas and completing the cycle [2]. Within drinking water distribution systems, nitrite may also form through the metabolic activity of *Nitrosomonas* bacteria, particularly under conditions of low oxygen availability and water stagnation in galvanized steel pipes. Additionally, the use of chloramine for residual disinfection may promote nitrite formation if treatment processes are inadequately controlled [5]. Major sources of nitrate and nitrite contamination in aquatic systems include agricultural practices – especially the application of synthetic fertilizers and manure – nitrogen-rich wastes from human activities, industrial emissions, and effluents from wastewater treatment facilities. Due to incomplete crop uptake, it is estimated that approximately 50% of applied fertilizer nitrogen may leach into soil, thereby increasing nitrate concentrations in surface and groundwater [5,6]. A thorough understanding of nitrate contamination sources is therefore essential for developing effective strategies to mitigate nitrate pollution [7].

Diet represents the primary source of nitrate exposure in humans, with vegetables such as spinach and beetroot accounting for approximately 80–90% of total intake. Drinking water contributes an estimated 15–20%, while other food sources, including animal-derived products, provide the remaining proportion. Nitrate metabolism involves the nitrate-nitrite-nitric oxide pathway, which depends on the oral microbiota and salivary glands. Following absorption in the stomach and small intestine, approximately 75% of ingested nitrate is excreted in urine, while up to 25% is actively concentrated in the salivary glands at levels up to tenfold higher than plasma concentrations. In the oral cavity, anaerobic bacteria located on the posterior tongue convert 5–7% of nitrate into nitrite, which is subsequently converted into nitric oxide in the stomach and systemically absorbed [8].

Although nitrates are generally considered to have low intrinsic toxicity, their metabolic conversion to nitrites may result in adverse health effects [9]. Nitrite exposure can induce methemoglobinemia, commonly referred to as "blue baby syndrome". In 2010, the International Agency for Research on Cancer classified nitrates and nitrites as Group 2A agents, indicating they are probably carcinogenic to humans [10]. Furthermore, nitrate and nitrite may serve as precursors for endogenous formation of genotoxic N-nitroso compounds, potentially increasing cancer risk when present in drinking water [9]. Beyond methemoglobinemia, the most consistent epidemiological evidence links nitrate exposure in drinking water to colorectal cancer, neural tube defects, and thyroid dysfunction, with some studies suggesting adverse effects even at concentrations below established regulatory limits [6]. Conversely, long-term exposure to nitrate exposure at permissible concentrations has shown inconsistent associations with bladder cancer risk [11].

Despite guidelines established by the World Health Organization (WHO) for safe nitrate and nitrite concentrations in drinking water, numerous countries continue to report exceedances, even in the absence of acute health effects such as methemoglobinemia or thyroid disorders [12]. Since the adoption of the Nitrates Directive, the European Union has prioritized the reduction of nitrate contamination in groundwater as major environmental and public health objective [13]. Regulatory limits for nitrate and nitrite vary slightly across international frameworks. European Union Directive 2020/2184 (EU) sets maximum values of 50 mg/L (11.3 mg/L as nitrogen) for nitrate and 0.5 mg/L (0.152 mg/L as nitrogen) for nitrite [14]. The United States Environmental Protection Agency (EPA) applies stricter limits, permitting 10 mg/L nitrate as nitrogen (44 mg/L nitrate) and 1 mg/L nitrite as nitrogen (3.3 mg/L nitrite) [15]. WHO guidelines recommend maximum concentrations of 50 mg/L for nitrate (11.3 mg/L as nitrogen) and 3 mg/L for nitrite (0.91 mg/L as nitrogen) [5]. In Serbia, national regulations are harmonized with these standards, establishing maximum allowable concentrations of 50 mg/L for nitrate (11.3 mg/L as nitrogen) and 0.03 mg/L for nitrite (0.009 mg/L as nitrogen) [16]. Notably, the Serbian nitrite limit is the most stringent among international standards, including those of the EU, WHO, and U.S. EPA.

The aim of this study was to evaluate nitrate and nitrite concentrations in untreated chlorinated drink-

ing water across the districts of the Autonomous Province of Vojvodina during 2023 and to assess the associated health risks for adults (≥18 years) and young children (≤5 years).

## Material and Methods

*Sampling and Analyses*

This investigation included 11,919 samples of unpurified chlorinated drinking water (NPCW) collected during 2023. All procedures - sampling, transport, and laboratory analysis - were conducted within seven authorized, certified, and accredited Public Health Institution laboratories operating in the territory of the Autonomous Province of Vojvodina.

Sampling locations were selected in accordance with stakeholder requirements (local governments and public utility companies) and formed part of the regular, scheduled drinking water health surveillance program. The sampling framework encompassed both urban and rural areas, as well as locations identified as having an increased contamination risk, particularly regions with intensive agricultural activity. Nitrate and nitrite concentrations were determined using accredited spectrophotometric analytical techniques. Sampling procedures followed internationally recognized standard: SRPS EN ISO 5667-1:2023, ISO 5667-3:2018, and SRPS ISO 5667-5:2008 [17–19]. Laboratory analyses were performed using accredited methods in compliance with ISO/IEC 17025 requirements by competent public health institutions responsible for drinking water safety monitoring [20,21]. For analytical results below the method detection limit, concentrations were modeled by assigning a value equal to one-half of the respective laboratory detection limit.

*Health Risk Assessment*

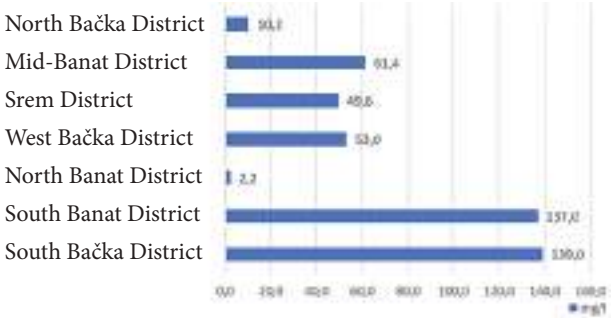
According to the US EPA, human health risk assessment is defined as a systemic process for estimating the likelihood and severity of adverse health effects resulting from exposure to hazardous substances [22]. In this study, non-carcinogenic health risks associated with nitrate and nitrite exposure were assesses using the Hazard Quotient (HQ) approach, following US EPA guidelines [23].

Exposure pathways included ingestion and dermal absorption from untreated chlorinated drinking water. Risk estimates were calculated for two population groups: children ≤ 5 years of age and adults ≥18 years. Demographic and exposure parameters were derived from data provided by the Statistical Office of the Republic of Serbia and relevant international sources.

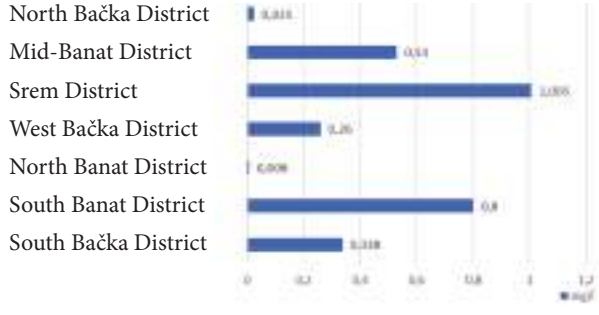
Quantitative health risk equations used for ingestion and dermal exposure pathways are presented in **Table 1.**

## Results and Discussion

Of the 11,919 NPCW samples analyzed, elevated nitrate concentrations were detected in 129 samples (1%), while elevated nitrite concentrations were identified in 456 samples (4%). The highest nitrate concentrations exceeding permissible limits were recorded in the South Bačka District (139 mg/l) and the South Banat District (137 mg/l). In contrast, the maximum nitrite concentration was observed in the Srem District (1.005 mg/l) **(Graphs 1 and 2)**.




**Graph 1**. Maximum nitrate concentrations by district




**Graph 2.** Maximum nitrite concentrations by district

**Table 1.** Quantitative health risk equation

| Pathway | Formula |
|---|---|
| Ingestion | CDI_ing = (Cw × IR × EF × ED)/(BW × AT) |
| Dermal | CDI_derm = (Cw × SA × PC × ET × EF × ED × CF)/(BW × AT) |
| Total CDI | CDI_tot = CDI_ing + CDI_derm |
| Hazard Index (HI) | HI = CDI_tot/RfD (or sum across contaminants) |

CDI ing – chronic daily intake by ingestion; Cw – concentration of contaminant in water; IR – ingestion rate; EF – exposure frequency; ED – exposure duration; BW – body weight; AT – Averaging time; CDI derm – chronic daily absorbed dose via dermal contact; SA – Skin surface area exposed; PC – Dermal permeability coefficient; ET – Exposure time; CF – volumetric conversion factor for water; RfD – Reference dose; HI – Hazard Index .

**Table 2.** Chronic hazard index for average and maximum nitrate and nitrite concentrations in drinking water for children up to 5 years old and adults over 18 years old in the territory of APV in 2023

| | Concentration (mg/L) | HI, after ingestion | HI, after dermal absorption | Total HI |
|---|---|---|---|---|
| For average nitrate concentration values | | | | |
| Children | 5.22 | 3.49E-01 | 1.98E-06 | 3.49E-01 |
| Adults | | 8.46E-02 | 3.77E-07 | 8.46E-02 |
| For average nitrite concentration values | | | | |
| Children | 0.0369 | 2.46E-03 | 1.40E-08 | 2.46E-03 |
| Adults | | 5.97E-04 | 2.71E-09 | 5.97E-04 |
| For maximum nitrate concentration values | | | | |
| Children | 139 | 9.27E+00 | 5.26E-05 | 9.27E+00 |
| Adults | | 2.25E+00 | 1.01E-05 | 2.25E+00 |
| For maximum nitrite concentration values | | | | |
| Children | 1.005 | 6.70E-02 | 3.80E-07 | 6.70E-02 |
| Adults | | 1.63E-02 | 7.37E-08 | 1.63E-02 |

HI – chronic hazard index; IR 1.6 L/day for children and 2 L/day for adults [15]; EF- 365 days/year; ET- 0.5 h/day [16]; ED- 5 years for children/75.61 years for adults [17]; BW- 15 kg for children [14] and 75.61 kg for adults; AT- ED*365 days [18]; RfD- 1.6 mg/kg/day [19]; SA- 1.815 $m^2$ for adults and 0.76 $m^2$ for children [20]; PC- 0.00001 m/hour [21]; ET- is specified as 0.5 hours/day for adults and children; CF for water is 0.001 L/$cm^3$ [21].

**Table 3.** Hazard Quotient for average and maximum concentrations of nitrates and nitrites in drinking water for children up to 5 years old and adults over 18 years old by districts of the Autonomous Province of Vojvodina in 2023

| District | Population | Concentration (mg/L) | HQ, after ingestion | HQ, after dermal absorption | Total HQ |
|---|---|---|---|---|---|
| South Bačka District | For average nitrate concentration values | | | | |
| | Children | 12.3 | 8.20E-01 | 4.65E-06 | 8.20E-01 |
| | Adults | | 1.99E-01 | 9.02E-07 | 1.99E-01 |
| | For average nitrite concentration values | | | | |
| | Children | 0.042 | 2.80E-03 | 1.58E-08 | 2.80E-03 |
| | Adults | | 6.79E-04 | 3.08E-09 | 6.79E-04 |
| | For maximum nitrate concentration values | | | | |
| | Children | 139 | 9.26E+01 | 5.25E-05 | **9.27E+00** |
| | Adults | | 2.25E+00 | 1.01E-05 | **2.25E+00** |
| | For maximum nitrite concentration values | | | | |
| | Children | 0.417 | 2.78E-02 | 1.57E-07 | 2.78E-02 |
| | Adults | | 6.74E-03 | 3.05E-08 | 6.74E-03 |
| West Bačka District | For average nitrate concentration values | | | | |
| | Children | 3.8 | 2.53E-01 | 1.43E-06 | 2.53E-01 |
| | Adults | | 6.14E-02 | 2.78E-07 | 6.14E-02 |
| | For average nitrite concentration values | | | | |
| | Children | 0.012 | 8.00E-04 | 4.53E-09 | 8.00E-04 |
| | Adults | | 1.94E-04 | 8.80E-10 | 1.94E-04 |
| | For maximum nitrate concentration values | | | | |
| | Children | 53 | 3.53E+00 | 2.00E-05 | **3.53E+00** |
| | Adults | | 8.57E-01 | 3.88E-06 | 8.57E-01 |
| | For maximum nitrite concentration values | | | | |
| | Children | 0.26 | 1.73E-02 | 9.83E-08 | 1.73E-02 |
| | Adults | | 4.20E-03 | 1.90E-08 | 4.20E-03 |
| Nort Bačka District | For average nitrate concentration values | | | | |
| | Children | 2.1 | 1.40E-01 | 7.94E-07 | 1.40E-01 |
| | Adults | | 3.40E-02 | 1.54E-07 | 3.40E-02 |
| | For average nitrite concentration values | | | | |
| | Children | 0.001 | 6.67E-05 | 3.78E-10 | 6.67E-05 |
| | Adults | | 1.62E-05 | 7.33E-11 | 1.62E-05 |
| | For maximum nitrate concentration values | | | | |
| | Children | 10.2 | 6.80E-01 | 3.85E-06 | 6.80E-01 |
| | Adults | | 1.65E-01 | 7.48E-07 | 1.65E-01 |
| | For maximum nitrite concentration values | | | | |
| | Children | 0.025 | 1.67E-03 | 9.45E-09 | 1.67E-03 |
| | Adults | | 4.04E-04 | 1.83E-09 | 4.04E-04 |

HQ – Hazard Quotient; IR 1.6 L/day for children and 2 L/day for adults [24]; EF – 365 days/year; ET – 0.5 h/day [25]; ED – 5 years for children/75.61 years for adults [26]; BW – 15 kg for children [27] and 75.61 kg for adults; AT- ED*365 days [28]; RfD – 1.6 mg/kg/day [29]; SA – 1.815 $m^2$ for adults and 0.76 $m^2$ for children [30]; PC – 0.00001 m/hour [31]; ET – is specified as 0.5 hours/day for adults and children; CF for water is 0.001 L/$cm^3$ [31].
**a** - Adult exposure duration (ED, years); North Bačka – 76.55; West Bačka – 74.6; South Bačka – 74.75; North Banat – 75.65; Central Banat – 75.25; South Banat – 75.65; Srem – 76.

For nitrates, the average HQ (combined ingestion and dermal exposure) for the adult population was 8.46E-02, which is below the threshold value of one and therefore considered acceptable. However, the maximum nitrate HQ reached 2.25E+00, exceeding the safety threshold and indicating a potential health risk **(Table 2).**

In the children's population (≤5 years), the average nitrate HQ was 3.49E-01, suggesting that average nitrate concentrations do not pose a health risk. In contrast,

**Table 4.** Hazard Quotient for average and maximum concentrations of nitrates and nitrites in drinking water for children up to 5 years old and adults over 18 years old by districts of the Autonomous Province of Vojvodina in 2023

| District | Population | Concentration (mg/L) | HQ, after ingestion | HQ, after dermal absorption | Total HQ |
|---|---|---|---|---|---|
| Srem District | For average nitrate concentration values | | | | |
| | Children | 3.6 | 2.40E-01 | 1.36E-06 | 2.40E-01 |
| | Adults | | 5.82E-02 | 2.64E-07 | 5.82E-02 |
| | For average nitrite concentration values | | | | |
| | Children | 0.0125 | 8.33E-04 | 4.72E-09 | 8.33E-04 |
| | Adults | | 2.02E-04 | 9.17E-10 | 2.02E-04 |
| | For maximum nitrate concentration values | | | | |
| | Children | 49.6 | 3.31 E+00 | 1.88E-05 | **3.31 E+00** |
| | Adults | | 8.02E-01 | 3.63E-06 | 8.02E-01 |
| | For maximum nitrite concentration values | | | | |
| | Children | 1.005 | 6.70E-02 | 3.80E-07 | 6.70E-02 |
| | Adults | | 1.63E-02 | 7.37E-08 | 1.63E-02 |
| South Banat District | For average nitrate concentration values | | | | |
| | Children | 5 | 3.33E-01 | 1.89E-06 | 3.33E-01 |
| | Adults | | 8.09E-02 | 3.66E-07 | 8.09E-02 |
| | For average nitrite concentration values | | | | |
| | Children | 0.011 | 7.33E-04 | 4.15E-09 | 7.33E-04 |
| | Adults | | 1.78E-04 | 8.07E-10 | 1.78E-04 |
| | For maximum nitrate concentration values | | | | |
| | Children | 137 | 9.13E+00 | 5.18E-05 | **9.13E+00** |
| | Adults | | 2.22E+00 | 1.00E-05 | **2.22E+00** |
| | For maximum nitrite concentration values | | | | |
| | Children | 0.8 | 5.33E-02 | 3.02E-07 | 5.33E-02 |
| | Adults | | 1.29E-02 | 5.86E-08 | 1.29E-02 |
| Central Banat District | For average nitrate concentration values | | | | |
| | Children | 3.36 | 2.24E-01 | 1.27E-06 | 2.24E-01 |
| | Adults | | 5.43E-02 | 2.46E-07 | 5.43E-02 |
| | For average nitrite concentration values | | | | |
| | Children | 0.06 | 4.00E-03 | 2.26E-08 | 4.00E-03 |
| | Adults | | 9.70E-04 | 4.40E-09 | 9.70E-04 |
| | For maximum nitrate concentration values | | | | |
| | Children | 61.43 | 4.10E+00 | 2.32E-05 | **4.10E+00** |
| | Adults | | 9.93E-01 | 4.50E-06 | 9.93E-01 |
| | For maximum nitrite concentration values | | | | |
| | Children | 0.53 | 3.53E-02 | 2.00E-07 | 3.53E-02 |
| | Adults | | 8.57E-03 | 3.88E-08 | 8.57E-03 |
| North Banat District | For average nitrate concentration values | | | | |
| | Children | 1.32 | 8.80E-02 | 4.99E-07 | 8.80E-02 |
| | Adults | | 2.13E-02 | 9.68E-08 | 2.13E-02 |
| | For average nitrite concentration values | | | | |
| | Children | 0.0052 | 3.47E-04 | 1.96E-09 | 3.47E-04 |
| | Adults | | 8.41E-05 | 3.81E-10 | 8.41E-05 |
| | For maximum nitrate concentration values | | | | |
| | Children | 2.2 | 1.47E-01 | 8.31E-07 | 1.47E-01 |
| | Adults | | 3.56E-02 | 1.61E-07 | 3.56E-02 |
| | For maximum nitrite concentration values | | | | |
| | Children | 0,008 | 5.33E-04 | 3.02E-09 | 5.33E-04 |
| | Adults | | 1.29E-04 | 5.86E-10 | 1.29E-04 |

HQ – Hazard Quotient; IR – 1.6 L/day for children and 2 L/day for adults [24]; EF – 365 days/year; ET – 0.5 h/day [25]; BW – 15 kg for children [27] and 75.61 kg for adults; AT-ED*365 days [28]; RfD – 1.6 mg/kg/day [29]; SA – 1.815 $m^2$ for adults and 0.76 $m^2$ for children [30]; PC – 0.00001 m/hour [31]; ET – is specified as 0.5 hours/day for adults and children; CF for water is 0.001 L/$cm^3$ [31].
**a** - Adult exposure duration (ED, years); North Bačka – 76.55; West Bačka – 74.6; South Bačka – 74.75; North Banat – 75.65; Central Banat – 75.25; South Banat – 75.65; Srem – 76.

the maximum nitrate HQ reached 9.27E+00, substantially exceeding the threshold of one and indicating a significant potential health risk for children **(Table 2).**

For nitrites, the HQ values for adults were 5.97E-04 for average concentration and 1.63E-02 for maximum concentrations. Both values are well below the threshold value of one, indicating no health risks **(Table 2).**

Similarly, in children, the HQ values for nitrites were 2.46E-03 (average) and 6.70E-02 (maximum), remaining below the safety threshold and suggesting no health risk from nitrite exposure in this age group **(Table 2).**

Across all scenarios, ingestion was identified as the dominant exposure pathway for both nitrate and nitrite, with dermal absorption contributing minimally to total exposure **(Table 2).**

District-level HQ analysis revealed that both adults and children are at increased risk associated with maximum nitrate concentrations in the South Bačka and South Banat districts. In contrast, in the West Bačka, Srem, and Central Banat districts, elevated risk was observed primarily for children, reflecting their higher susceptibility to nitrate exposure **(Tables 3 and 4).**

Overall, HQ values indicate that average nitrate and nitrite exposures are safe for both children and adults across the Autonomous Province of Vojvodina. However, maximum nitrate concentrations – particularly in specific districts – exceed acceptable risk thresholds, underscoring the importance of incorporating HQ-based risk management into routine drinking water safety evaluation and management strategies.

## Discussion

Comparison of the present findings with international data indicates that nitrate contamination of drinking water remains a widespread concern across Europe and beyond. According to the European Environment Agency, all 27 European Union Member States report groundwater bodies with nitrate concentrations exceeding 50 mg/L. Moreover, a substantial proportion of groundwater monitoring stations in Spain, Portugal, Germany, Malta, Luxembourg, Cyprus, and Belgium record nitrate levels above the maximum allowable concentration [13]. Water quality assessments further identify the Czech Republic, the Netherlands, and Slovenia as countries facing particularly severe challenges, with 70%-90% of monitored water bodies classified as poor quality [9]. In England, approximately 55% of the national territory has been designated as a Nitrate Vulnerable Zone, primarily due to elevated nitrate concentrations in groundwater and rivers [32].

A broader international comparison reveals considerable variability in nitrate and nitrite concentrations. Notably, Poland and Malta reported high average nitrate concentrations of 41.2 mg/L and 58.1 mg/L, respectively, with Poland reaching the maximum value of 194.8 mg/L. In the same study, the average nitrite concentration in Poland was 0.044 ± 0.036 mg/L, with a maximum recorded value of 0.123 mg/L. Marked regional differences were also observed in the United Kingdom, where England exhibited an average nitrate concentration of 22.94 mg/L, compared with a substantially lower average of 2.07 mg/L in Scotland. In Morocco, the reported average nitrate concentration was 24.73 mg/L, with maximum values reaching 82.02 mg/L [27].

Data from Serbia underscore the magnitude of the problem. In 2014, drinking water analyses conducted in rural areas near Požarevac identified nitrate and nitrite as the principal causes of unsafe water quality, with nitrate concentrations reaching 1138.9 mg/dm$^3$ and nitrite concentrations up to 0.40 mg/dm$^3$ [33]. A 2019 study conducted across settlements in the South Bačka Administrative District detected exceedances of permissible nitrite concentrations in 23 of 386 samples (5.96%) of untreated chlorinated water [9]. More, recently, in 2022, elevated nitrite concentrations were identified as a major hazard in the Autonomous Province of Vojvodina, occurring in 13% of unpurified chlorinated water samples [34]. In 2023, 783,104 individuals, representing approximately 45% of the total population of Vojvodina, were supplied with non-purified but disinfected drinking water [35].

In contrast to concentration-based monitoring, relatively limited research has focused on health risk characterization using the Hazard Quotient. Nevertheless, studies from several countries highlight the value of this approach. In Turkey, groundwater investigations in Mersin Province demonstrated generally low overall risk but identified localized areas – particularly between Tarsus and Çeşmeli – where HQ values exceeded 4.00, indicating a significant health risk for children [36]. Similarly, in Italy, health risk assessments conducted in the Poirino Plateau revealed substantially higher risks for children, primarily through oral exposure pathways, compared with dermal exposure, particularly in areas affected by nitrate-contaminated shallow aquifers [37]. Comparable findings have been reported in Poland, where a study assessing nitrate ingestion risk found that 50% of the analyzed samples posed an unsafe HQ (>1) for children, compared with 40% for adolescents and 33% for adults. Reported HQ values reached 6.90 for children and 4.87 for adolescents, indicating pronounced age-related vulnerability. Studies from Iran and China further corroborate these concerns, with reported HQ values for children in China reaching as high as 19.86

[27]. Although drinking water safety in the Republic of Serbia is regulated by national legislation defining mandatory analytical parameters, monitoring frequency, and permissible limit values, formal health risk assessment methodologies are not yet integrated into routine regulatory practice [38]. Alignment with international standards requires strengthening national capacities, improving healthcare financing strategies, and harmonizing regulatory frameworks with regional and global best practices [39]. In this context, the implementation of chronic hazard index-based approaches is essential for identifying localized high–risk areas and supporting evidence-based prioritization of mitigation measures. Effective management of nitrate and nitrite contamination necessitates an integrated, multidisciplinary approach. Such strategies should account for local environmental conditions and include optimized fertilizer application practices based on soil testing, promotion of natural attenuation processes such as denitrification and plant uptake, and, where necessary, the implementation of appropriate of water purification technologies [40].

Several limitations of this study should be acknowledged. First, the risk assessment was limited to children under 5 years of age and adults over 18 years, excluding other potentially vulnerable population groups. Second, the study did not evaluate the combined health risk associated with nitrate-nitrite metabolic conversion, which may underestimate total exposure-related risk. Finally, the assessment considered only drinking water exposure and did not account for total dietary intake, which represents an important additional source of nitrate and nitrite exposure.

## Conclusion

The findings of the present study clearly demonstrate a significant public health concern in specific regions of the Autonomous Province of Vojvodina, where maximum Hazard Quotient values for nitrates exceed established safety thresholds. Elevated maximum nitrate concentrations are associated with increased health risk for both children under 5 years of age and adults over 18 years. The results further confirm that ingestion is the predominant exposure pathway for nitrate and nitrite in both population groups, while dermal absorption contributes minimally to overall risk. Beyond emphasizing the importance of drinking water purification, these findings highlight the urgent need for systemic incorporation of health risk assessment methodologies into routine drinking water monitoring and regulatory frameworks.

Future research should prioritize the integration of health risk assessment into legislative and professional practice and support development of a unified national database linking drinking water quality parameters with health statistics data at the national, provincial, district, and local levels.

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Rad je primljen 21. X 2025.
Recenziran 12. XI 2025.
Prihvaćen za štampu 18. XII 2025.
BIBLID.0025-8105:(2025):LXXVIII:9-12:235-242.

Med Pregl 2025; LXXVIII (9-12): 243-250. Novi Sad: septembar-decembar.

# EARLY NEUROLOGICAL RECOVERY AFTER ANTERIOR CERVICAL DISCECTOMY WITH CAGE FUSION

# *RANI NEUROLOŠKI OPORAVAK NAKON PREDNJE CERVIKALNE DISKEKTOMIJE SA KEJDŽ-FUZIJOM*

**Srđan STANKOVIĆ[1], Sara AZARIĆ[1], Dragana TEŠIĆ[1], Snežana ZORIĆ[1], Veljko PANTELIĆ[1, 2] and Đula ĐILVESI[1, 2]**

ORCID NUMBER
Srđan Stanković – ORCID: 0009-0002-7750-9051
Sara Azarić – ORCID: 0009-0008-8773-5785
Dragana Tešić – ORCID: 0009-0008-9535-638X
Snežana Zorić – ORCID: 0009-0005-7229-7178
Veljko Pantelić – ORCID: 0009-0008-1875-3592
Đula Đilvesi – ORCID: 0000-0003-3131-7855

University of Novi Sad, Faculty of Medicine Novi Sad[1]
University Clinical Centre of Vojvodina, Novi Sad
Department of Neurosurgery[2]

Original study
*Originalni naučni rad*
UDK 616.711-089.87:[616.8:615.8
https://doi.org/10.2298/MPNS2512243S

**Abstract**

**Introduction.** Anterior cervical discectomy and fusion is the standard surgical treatment for cervical discopathy and myelopathy caused by degenerative disc disease and osteophyte formation. The primary goal of the procedure is decompression of neural structures within the spinal canal by removing compressive pathology. Although neurological recovery after the procedure has been widely studied, data on neurological status in the immediate postoperative period remain limited. This retrospective study analyzed the association between clinical and radiological characteristics and early postoperative neurological recovery following the surgery. **Material and Methods.** The study included 66 patients who underwent the procedure at the Clinical Center of Vojvodina between 2022 and 2023. Statistical analysis using the $\chi^2$ test and Fisher's exact test ($p<0.05$) evaluated the influence of neurological deficit type, number of operated levels, presence of spondylosis, and type of disc pathology on early postoperative neurological outcome. **Results.** Overall neurological improvement was observed in 82.5% of patients, with 42.8% showing significant improvement and 39.7% mild improvement. Statistically significant difference in early neurological recovery was found between single-level and two-level procedures ($p=0.005$), as well as between patients with disc protrusion and those with disc extrusion ($p=0.035$). No significant association was identified between early neurological recovery and neurological deficit type or the presence of spondylosis. **Conclusion.** Disc protrusion and a lower number of operated levels are positive predictors of early neurological improvement after the procedure, whereas spondylosis and neurological deficit type do not significantly affect early outcomes. Early postoperative neurological assessment may provide valuable insight into overall functional recovery.

**Key words:** Neurological Rehabilitation; Diskectomy; Cervical Vertebrae; Spinal Fusion; Intervertebral Disc Displacement; Spondylosis; Decompression, Surgical; Recovery of Function

**Sažetak**

**Uvod.** Prednja cervikalna diskektomija i fuzija predstavlja standardni hirurški postupak u lečenju cervikalnih diskopatija i mijelopatija uzrokovanih degenerativnim promenama diska i osteofitima. Njena osnovna uloga je da izvrši dekompresiju nervnih struktura kičmenog kanala uklanjanjem tkiva koje ih komprimuje. Iako je prisutan veliki broj radova koji prate neurološki oporavak pacijenata nakon ove procedure, nema studija koje su se fokusirale na neurološki status operisanih u najranijem postoperativnom periodu, te je cilj ove retrospektivne studije bio da ispita povezanost kliničkih i radioloških karakteristika pacijenata sa ranim postoperativnim neurološkim oporavkom nakon ove procedure. **Materijal i metode.** Analizirano je 66 pacijenata operisanih u Kliničkom centru Vojvodine tokom 2022-2023. godine. Statističkom analizom ($\chi^2$ test, Fišerov tačan test, $p < 0,05$) ispitivan je uticaj tipa neurološkog ispada, broja operisanih nivoa, prisustva spondiloze i tipa oštećenja diska na rani postoperativni neurološki ishod. **Rezultati.** U našoj studiji je 82,5% pacijenata ostvarilo poboljšanje neurološkog statusa (42,8% značajno, 39,7% blago). Nađena je statistički značajna razlika između broja pacijenata koji su postigli rani neurološki oporavak kada je procedura urađena na jednom nivou u odnosu na dva nivoa ($p = 0,005$), kao i između onih sa protruzijom u poređenju sa ekstruzijom diska ($p = 0,035$). Nije utvrđen značajan uticaj tipa neurološkog ispada niti prisustva spondiloze na rani neurološki oporavak. **Zaključak.** Protruzija diska i manji broj operisanih nivoa su pozitivni prediktori ranog neurološkog poboljšanja nakon navedene procedure, dok spondiloza i tip neurološkog deficita ne utiču značajno na ishod. Praćenje ranog postoperativnog perioda ima klinički značaj jer može doprineti predviđanju ukupnog funkcionalnog oporavka pacijenata.

**Ključne reči:** neurološka rehabilitacija; diskektomija; vratni pršljenovi; spinalna fuzija; protruzija diska; spondiloza; hirurška dekompresija; oporavak funkcije

## Introduction

Anterior cervical discectomy and fusion (ACDF) is among the most frequently performed procedures in cervical spine surgery [1]. The primary indications for ACDF include cervical intervertebral disc herniation and osteophyte formation at the intervertebral level. In both conditions, progressive degenerative changes lead to a reduction in cervical spinal canal volume, resulting in compression of the spinal cord and spinal nerve roots [1–3]. Consequently, patients may develop neurological syndromes such as cervical radiculopathy and degen-

✉ Corresponding author: Srđan Stanković, E-mail: stankov.srdjan995@gmail.com, djula.djilvesi@mf.uns.ac.rs

***Abbreviations***

| | |
|---|---|
| ACDF | – anterior cervical discectomy and fusion |
| CNS | – central nervous system |
| MRI | – magnetic resonance imaging |
| PEEK | – polyetheretherketone |
| P25 | – 25th percentile |
| P75 | – 75th percentile |
| $\chi^2$ | – chi-square test |

erative cervical myelopathy, clinically manifested by neck and upper extremity pain, numbness, impaired coordination, and sphincter control issues [4,5]. Definitive treatment of these conditions requires surgical decompression of the spinal canal through removal of the compressive pathology, followed by restoration of segmental stability – principles that constitute the foundation of ACDF [1,6]. During the procedure, the intervertebral disc and associated osteophytes are excited, and the resulting intervertebral space is reconstructed using a prefabricated cage or bone graft, thereby achieving stabilization of the affected cervical segment [6–8]. Additional anterior plate fixation may be employed depending on surgeon preference and biomechanical requirements [6]. Postoperative management typically involves early mobilization and kinesitherapy with temporary cervical orthosis support until radiographic evidence of intervertebral fusion is obtained, after which the orthosis is discontinued and rehabilitation intensified [9]. Despite the development of motion-preserving alternatives, such as cervical disc arthroplasty, and minimally invasive techniques, including endoscopic decompression and discectomy, ACDF continues to be regarded as the "gold standard" for the surgical management of cervical disc disease due to its reliability and favorable long-term outcomes [10,11]. However, successful postoperative stability and prevention are strongly influenced by the quality of intervertebral fixation and fusion [12]. To achieve this, various grafting options have been employed, including autologous bone graft, allografts, and synthetic interbody cages [13,14]. Each approach presents specific advantages and limitations. Autologous bone grafts – most commonly harvested from the iliac crest – are associated with donor-site morbidity such as hematoma, seroma, infection, and in rare cases, iliac fracture, hemorrhage, or herniation of abdominal contents [13,15]. Allografts, while avoiding donor-site complications, carry a potential risk of disease transmission. As a result, contemporary surgical practice increasingly favors synthetic cages, which eliminate donor-site morbidity [16].

Currently, interbody cages are most commonly manufactured from polyetheretherketone (PEEK), carbon fiber, or titanium [13]. These materials allow combination with osteoconductive and osteoinductive adjuncts, including bone shavings from osteophytes, bone marrow aspirate, platelet-rich plasma, or bone morphogenetic proteins, thereby facilitating osseous integration and fusion [17–19]. Advances in cage design and biomedical technology have significantly improved ACDF outcomes over recent decades by reducing complication rates and enhancing cervical spine biomechanics [20,21]. Nevertheless, although numerous studies have evaluated long-term neurological outcomes and complication profiles following ACDF, the early postoperative neurological recovery period – prior to the initiation of formal rehabilitation – remains insufficiently investigated. Emerging evidence suggests that early neurological improvement is not merely a transient phenomenon but may correlate with long-term functional and neurological outcomes after spinal decompression procedures [22]. Therefore, early postoperative neurological status may represent an important prognostic indicator, reflecting the immediate effectiveness of neural decompression and the residual capacity for neurological recovery. Moreover, many studies assessing postoperative outcomes following cervical spine surgery do not adequately consider the influence of individual patient and pathology-related characteristics. Factors such as the presence of degenerative cervical changes, the number of operated levels, and the type or severity of disc pathology may significantly affect postoperative recovery. This consideration is particularly relevant given that chronic compressive injury to the spinal cord and nerve roots results in axonal damage, and axonal regeneration within the central nervous system (CNS) is limited [23–25].

The aim of this study was to investigate the relationship between selected patient and disease-related characteristics and early postoperative neurological recovery following ACDF. Based on previous studies examining neurological outcomes after ACDF [26–28] and our clinical experience, we analyzed the following parameters as potential predictors of early neurological recovery:

- type of preoperative neurological deficit,
- number of operated cervical levels,
- presence of cervical spondylosis,
- type of intervertebral disc lesion.

## Material and Methods

This study was designed as a retrospective observational analysis using data obtained from the Clinical Information System of the Clinical Center of Vojvodina. The study population comprised 66 patients who underwent ACDF at the Clinic for Neurosurgery, Clinical Center of Vojvodina, between January 1, 2022, and December 31, 2023. The study protocol was approved by the Ethics Committee of the Clinical Center of Vojvodina.

Data were collected from patients' medical records, including preoperative and postoperative neurosurgical assessments, radiological imaging (X-ray and MRI), operative reports, discharge summaries, and available documentation from institutions where inpatient rehabilitation was conducted. In cases where specific documentation was unavailable, patients were excluded only from statistical analyses requiring the missing data; such exclusions are specified in the Results section. Radiological findings were interpreted according to official radiology reports. When detailed radiological descriptions were unavailable, the presence of degenerative cervical spine changes (cervical spondylosis) was determined based on established diagnostic criteria described in the literature [29].

The observation period for evaluating postoperative neurological changes was defined as the interval from immediately after surgery until the initiation of formal rehabilitation. This approach was chosen to minimize the influence of physical therapy and biological remyelination process on neurological recovery. Remyelination of chronically compressed spinal nerve roots may take up to eight weeks [30], which exceeds the typical timeframe before rehabilitation begins. Accordingly, this observation window was intended to isolate the direct effect of surgical decompression, primarily reflecting the removal of functional axonal conduction block.

Early neurological recovery was defined as any improvement in neurological status compared with the preoperative condition within this timeframe. Neurological status was assessed by comparing preoperative findings with postoperative neurological descriptions documented in neurosurgical discharge summaries and initial rehabilitation assessments. Based on these evaluations, postoperative neurological outcomes were categorized as follows:

– Significant improvement: complete resolution or marked reduction of neurological signs and symptoms, confirmed by concordance between patient self-report and objective neurological examination;

– Mild improvement: partial symptom regression or reduced symptom intensity, typically reported subjectively by the patient and accompanied by minor or inconsistent objective neurological changes;

– No significant improvement: absence of measurable neurological change compared with the preoperative status.

These outcome categories were subsequently used for statistical analyses.

Data were presented as mean ± standard deviation, median with interquartile range (P25–P75), or absolute and relative frequencies, depending on data distribution and variable type. Descriptive statistics included patient sex and age, presenting symptoms, type of preoperative neurological deficit (radiculopathy or myelopathy), presence of cervical spondylosis, number of operated levels (single-level or two-level ACDF), distribution of disc pathology by cervical level, time from hospital discharge to initiation of rehabilitation, and early postoperative neurological outcome.

Comparative analyses were performed to evaluate associations between early neurological recovery and selected clinical and radiological parameters. Early recovery (mild or significant improvement) was compared between the following subgroups:

– radiculopathy vs. myelopathy;
– single-level vs. two-level ACDF;
– presence vs. absence of cervical spondylosis;
– disc protrusion vs. disc extrusion.

Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Additionally, the association between the number of operated levels and postoperative complications was assessed by comparing complication rates between single- and two-level ACDF groups using the Chi-square test. All statistical analyses were performed using SPSS Statistics 23 (IBM Corp., Armonk, NY, USA). A value of $p<0.05$ was considered statistically significant.

## Results

A total of 66 patients were included in the study, comprising 35 men (53%) and 31 women (47%). The mean patient age was 52.20 ± 11.84 years (range: 23-79 years) **(Table 1).**

The most frequently reported presenting symptoms were neck pain (32 patients), bilateral upper limb weakness (29 patients), bilateral upper limb numbness (25 patients), and unilateral upper limb tingling (21 patients), with an almost equal distribution between the right and left sides (11 vs. 10 patients). Less common symptoms included concurrent upper limb weakness and pain (15 patients each), gait disturbance (11 patients), and lower limb tingling (9 patients). Isolated lower limb weakness was reported by 21 patients. Other symptoms - such as headache, dizziness, sphincter dysfunction, hand or foot spasms, and unilateral sensory or motor deficits of the lower extremities - were present in 7 patients.

Preoperative neurological assessment revealed isolated cervical radiculopathy in 21 patients (32%), cervical myelopathy in 25 patients (40%), and combined radiculopathy and myelopathy in 19 patients (29.2%). There was no statistically significant difference between the number of patients with isolated radiculopathy and those with isolated myelopathy ($\chi^2 = 0.348$; df = 1; p = 0.555). One patient was excluded

**Table 1.** Basic demographic characteristics of patients (N=66); preoperative neurological deficit type (N=65); radiographic findings of cervical spine spondylosis (N=60)

| | |
|---|---|
| Age (years), Mean ± SD | 52.20±11.84 |
| Sex, Male/Female n (%) | 35 (53)/31 (47) |
| Neurological deficit type (N=65) | |
| Radiculopathy, n (%) | 21 (32.3) |
| Myelopathy, n (%) | 25 (38.5) |
| Concurrent neurological deficits; n (%) | 19 (29.2) |
| Single-level disc damage | 47 (71.2) |
| Two-level disc damage | 19 (28.8) |
| Radiological finding of spondylosis in adjacent vertebrae (N=60), n (%) | |
| Severe | 37 (61.7%) |
| Mild | 12 (20%) |
| No spondylosis | 11 (18.3%) |

N – sample size (number of patients); SD – standard deviation

from further neurological analysis because surgery was indicated solely on MRI findings of a disc extrusion, with headache as the only symptom and no documented neurological deficit (final n = 65).

Perioperative radiological documentation (X-ray and/or MRI) was available for 60 patients; imaging data were unavailable for 6 patients. These cases were excluded only from analyses requiring radiological variables. No systematic differences in clinical characteristics were observed between patients with complete and incomplete imaging data.

Radiographically evident degenerative cervical spine changes were present in 37 patients (61.7%), while mild degenerative changes were observed in 12 patients (20%), and no degenerative changes in 11 patients (18.3%). The prevalence of radiographically confirmed spondylosis was significantly higher compared to mild or absent degenerative changes ($\chi^2$ = 18.333; df = 1; p = 0.000; $\chi^2$ = 21.324; df = 1; p = 0.000).

Single-level ACDF was performed in 47 patients (71.2%), whereas 19 patients (28.8%) underwent two-level ACDF. Patients who underwent three–level ACDF were not analyzed separately due to their very small number during the study period, which precluded meaningful statistical comparison. Inclusion of three-level procedures in the two-level group was deliberately avoided to preserve group homogeneity with respect to surgical extent and biomechanical considerations.

Among single-level procedures, disc protrusion/extrusion was most commonly located at the C5–C6 level (19/47; 40.4%). In the two-level group, adjacent disc involvement was observed in nearly all cases (18/19; 94.7%), with disc herniation most frequently located at C5–C6 and C6–C7 levels.

Postoperative rehabilitation data were available for 26 patients. Half of these patients initiated inpatient rehabilitation within 15 days following discharge from the neurosurgery clinic, while 7 patients (26.9%) began rehabilitation more than 30 days after discharge. The median duration of rehabilitation was 21 days (range: 14–21), indicating that approximately one-quarter of patients underwent rehabilitation lasting three weeks **(Table 2).**

Due to incomplete documentation, two patients were excluded from the neurological outcome analysis, was along with one patient without preoperative neurological deficit, resulting in a final sample size of 63 patients.

Significant neurological improvement was observed in 27 patients (42.8%), mild improvement in 25 patients (39.7%), and no meaningful improvement in 11 patients (17.5%). The proportion of patients without neurological improvement was significantly

**Table 2.** Description of early postoperative neurological status; period from discharge to the initiation of inpatient rehabilitation and duration thereof

| Postoperative neurological status (N=63) | |
|---|---|
| No significant improvement | 11 (17.5) |
| Mild improvement | 25 (39.7) |
| Significant improvement | 27 (42.8) |
| Initiation of rehabilitation (days after surgery); Median (P25–P75) | 14 (10-30) |
| Duration of rehabilitation; Median (P25–P75) | 21 (14-21) |

N – sample size (number of patients); SD – standard deviation; P25 – 25th percentile; P75 – 75th percentile

**Table 3.** Effect of the analyzed parameters on early postoperative neurological recovery; n (%)

| | No improvement (n=11) [a] | Mild improvement (n=25) [b] | Significant improvement (n=27) [c] | Significance[#] |
|---|---|---|---|---|
| Type of isolated preoperative neurological deficit (N=45): | | | | |
| Radiculopathy, (n=21) | 3 (14.3) | 11 (52.4) | 7 (33.3) | b/a***; c/a**,# |
| Myelopathy, (n=24) | 5 (20.8) | 11 (45.8) | 8 (33.4) | c/a***; b/a*,# |
| Single-level disc damage | 9 (20) | 15 (33.3) | 21 (46.7) | c/a***,# |
| Two-level disc damage | 3 (15.8) | 10 (52.6) | 6 (31.6) | b/a***; c/a*,# |
| Spondylosis of adjacent vertebrae | | | | |
| With spondylosis | 10 (27.8) | 13 (36.1) | 13 (36.1) | ns[#] |
| Mild spondylosis | - | 6 (50) | 6 (50) | ns[#] |
| No spondylosis | 1 (9.1) | 4 (36.4) | 6 (54.5) | b,c/a***,# |
| Radiological finding of single-level disc damage | | | | |
| Extrusion | 7 (18.4) | 12 (31.6) | 19 (50) | c/a***; c/b*,# |
| Protrusion | 1 (16.7) | 3 (50) | 2 (33.3) | b/a***; c/a*,# |
| Radiological finding of two-level disc damage – upper disc | | | | |
| Extrusion | 3 (27.3) | 5 (45.4) | 3 (27.3) | b/a,c*,# |
| Protrusion | - | 5 (62.5) | 3 (37.5) | b/c**,# |
| Radiological finding of two-level disc damage – lower disc | | | | |
| Extrusion | 3 (25) | 6 (50) | 3 (25) | b/a,c**,# |
| Protrusion | - | 4 (57.1) | 3 (42.9) | ns[#] |

# Chi-square test and Fisher's exact test; *p<0.05; **p<0.01; ***p<0.001; ns – not statistically significant

lower compared with those who achieved significant improvement ($\chi^2 = 8.719$; df = 1; p = 0.003) or mild improvement ($\chi^2 = 6.918$; df = 1; p = 0.008) **(Table 2).**

*Influence of Neurological Deficit Type*

Only patients with a single preoperative neurological deficit (radiculopathy or myelopathy) were included in this analysis (n = 45). Among patients with radiculopathy (n = 21), 3 (14.3%) showed no improvement, 11 (52.4%) mild improvement, and 7 (33.3%) significant improvement. Among patients with myelopathy (n = 24), 5 (20.8%) showed no improvement, 11 (45.8%) mild improvement, and 8 (33.4%) significant improvement. Although both groups demonstrated a significantly higher proportion of improved compared with unimproved patients, no statistically significant difference in recovery distribution was observed between radiculopathy and myelopathy groups ($\chi^2 = 0.1895$; df = 1; p = 0.6637) **(Table 3).**

*Influence of Number of Operated Levels*

Among patients undergoing single-level ACDF (n = 45), significant improvement was observed in 21 patients (46.7%), mild improvement in 15 patients (33.3%), and no improvement in 9 patients (20%). In the two-level ACDF group (n = 19), 6 patients (31.6%) achieved significant improvement, 10 (52.6%) mild improvement, and 3 (15.8%) showed no improvement. A statistically significant association was found between the number of operated levels and early postoperative neurological recovery ($\chi^2 = 10.526$; df = 2; p = 0.005) **(Table 3).**

*Influence of Cervical Spondylosis*

Among patients with radiographically confirmed cervical spondylosis (n = 36), significant neurological recovery occurred in 13 patients (36.1%), mild improvement in 13 patients (36.1%), and no improvement in 10 patients (27.8%) **(Table 3).** Although postoperative improvement was statistically significant in patients without spondylosis, no significant correlation was identified between the presence or severity of cervical spondylosis and the degree of early neurological recovery ($\chi^2 = 4.663$; df = 4; p = 0.097).

*Influence of Disc Lesion Type*

The distribution of disc protrusion and extrusion is presented in **Table 3**. In all two-level ACDF cases, both operated discs demonstrated the same lesion type. In both single- and two-level ACDF groups, improved neurological outcomes were significantly more frequent than absence of improvement **(Table 3).** A statistically significant difference in early postoperative neurological recovery was observed between patients with disc protrusion and those with disc extrusion, with better outcomes of the protrusion group ($\chi^2 = 6.674$; df = 2; p = 0.035).

**Discussion**

The introduction of PEEK cages for ACDF has led to substantial improvements in postoperative outcomes, both by enhancing segmental stability and by reducing procedure-related complications [13,15]. Traditional bone grafts, which were once the predominant material used in ACDF, were susceptible to dislocation due to their flat contact surfaces and often required supplementary anterior plate fixation. This additional hardware increased the risk of intraoperative and delayed complications [31,32]. In contrast, PEEK cages are distinguished with irregular, serrated surfaces that reduce the likelihood of dislocation and minimize the need for additional fixation [32]. Consequently, ACDF using cage-based techniques is now regarded as a relatively safe procedure. Nevertheless, this does not diminish the importance of identifying patient- and pathology-related risk factors that may influence surgical outcomes.

The present study focused specifically on the early postoperative period following ACDF, defined as the interval from surgery to the initiation of inpatient rehabilitation (median: 21 days). This timeframe is often underrepresented in the literature, as most studies concentrate on long-term neurological recovery, fusion/stabilization rates, and late complications [33–35]. However, from a patient-centered perspective, persistent neurological symptoms in the immediate postoperative period may substantially affect quality of life, psychological well-being, and engagement in rehabilitation [36]. Early postoperative neurological status must therefore play a critical role in shaping the overall recovery trajectory.

Evidence from lumbar spine surgery supports this concept. Studies on lumbar microdiscectomy have demonstrated that early postoperative pain relief and neurological improvement strongly predict long-term surgical success, despite differences in anatomical region and pathology [37]. Similarly, longitudinal studies monitoring neurological recovery after spinal cord decompression have shown a significant correlation between the severity of residual postoperative symptoms and final functional outcomes [38,39]. These findings reinforce the clinical relevance of identifying factors that influence early neurological recovery after ACDF.

The age distribution of our cohort was heterogeneous, ranging from 23 to 79 years, with a mean age of 52.20 ± 11.84 years. This supports existing evidence that cervical disc disease predominantly affects older individuals. Progressive deterioration of intervertebral discs with aging is well documented and is largely attributed to chronic mechanical stress [40]. Such stress induces myxomatous degeneration of the annulus fibrosus, leading to collagen fiber disorganization and cyst formation, which weaken the posterior disc wall and predispose it to herniation into the spinal canal - particularly in the lordotic cervical spine [41]. The dynamic cervical spine model by Sadegh and Tchako demonstrated that maximal stress concentrations typically occur between the C4 and C6 vertebral levels, corresponding to the apex of the cervical lordosis (Cobb angle) [42]. In line with these observations, the C5–C6 level was the most frequently operated segment in our study.

In our cohort, isolated cervical radiculopathy and myelopathy were nearly equally represented. We did not observe a statistically significant difference in early postoperative neurological recovery between these two groups. This finding contrasts with some reports, such as that of Toci et al. [43], who described more pronounced early motor recovery in patients with myelopathy. However, those authors also noted that minimal overall clinical improvement was more common in patients with radiculopathy and that differences were not significant when stricter outcome criteria were applied. Given these inconsistencies, it appears likely that early and late neurological recovery are more strongly influenced by the degree and duration of neural compression, as well as preoperative symptom severity, rather than by the specific type of neurological deficit alone [44,45].

A high proportion of patients in our study (81.7%) demonstrated radiographically evident cervical spondylosis, with pronounced degenerative changes observed in 61.7%. Despite this, we found no significant association between the presence or severity of spondylosis and early postoperative neurological recovery. This finding is consistent with observations by Lehmann et al. [46], who reported that new or persistent neurological deficits after ACDF may occur at cervical levels other than the operated segment. Such deficits may be attributed to multilevel degenerative changes and dermatomal overlap caused by progressive spondylosis at adjacent or distant levels. Notably, the prevalence of spondylosis in their cohort was 2.5 times lower than in ours, yet similar conclusions were reached. Collectively, these findings suggest that the extent of spondylotic degeneration alone is not a reliable predictor of early or delayed neurological recovery.

In contrast, the type of disc lesion emerged as a significant determinant of early postoperative neurological outcome. Patients with disc protrusion demonstrated significantly better early neurological recovery compared to those with disc extrusion. This finding was clinically intuitive, as disc extrusion represents a more advanced pathological state associated

with greater spinal canal compromise and more severe neural compression. Previous studies have consistently shown that the extent of compression is inversely related to the potential of neurological recovery, particularly in the early postoperative period [44,45].

## Conclusion

This study demonstrated that disc protrusion is a statistically significant predictor of more favorable early postoperative neurological recovery following anterior cervical discectomy and fusion compared with disc extrusion. Additionally, the number of operated levels was significantly associated with early neurological improvement, as well as with the incidence of postoperative complications. In contrast, neither the type of neurological deficit nor the presence of cervical spondylosis showed a significant correlation with early postoperative neurological recovery.

Considering these findings, together with the inherent limitations of a retrospective study design, we emphasize the clinical importance of systematic assessment of early postoperative neurological status in patients undergoing Anterior Cervical Discectomy and Fusion. Early recovery may reflect the immediate effectiveness of neural decompression and may serve as important prognostic indicator for long-term functional outcomes. Identification of factors influencing this critical postoperative period may help optimize patient counseling, rehabilitation strategies, and overall surgical management.

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Rad je primljen 13. XI 2025.
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# EFFICACY OF MOLNUPIRAVIR IN COVID-19 INFECTION TREATMENT

## *EFIKASNOST MOLNUPIRAVIRA U LEČENJU COVID-19 INFEKCIJE*

**Vedrana PETRIĆ[1,2], Maria PETE[1,2], Aleksandra PASTORNAČKI[1], Nina ĐURIĆ[1], Vanja VLATKOVIĆ[1] and Tamara SIMEUNOVIĆ[1]**

ORCID NUMBER
Vedrana Petrić – 0000-0003-4283-0363
Maria Pete – 0000-0002-1772-5564
Aleksandra Pastornački – 0009-0004-3636-5949
Nina Đurić – 0009-0008-6312-7742
Vanja Vlatković – 0009-0003-0415-2060
Tamara Simeunović – 0009-0007-1696-9704

University Clinical Center of Vojvodina, Novi Sad
Clinic for Infectious Diseases[1]
University of Novi Sad, Faculty of Medicine, Novi Sad
Department for Infectious Diseases[2]

Original study
*Originalni naučni rad*
UDK 616.98:578.834]:615.281.8.03
https://doi.org/10.2298/MPNS2512251P

**Abstract**
**Introduction**. Molnupiravir is an orally administered antiviral agent approved for the treatment patients with mild to moderate coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2. Its antiviral effect is based on the inhibition of viral replication. The aim of this study was to evaluate the effectiveness and safety of molnupiravir in clinical practice. **Material and Methods**. This retrospective study included 74 non-hospitalized patients with mild to moderate clinical presentation who were treated with molnupiravir at the Covid Hospital of the University Clinical Center of Vojvodina during 2022. Treatment efficacy was assessed based on the occurrence of hospitalization or death within 28 days after therapy initiation. **Results**. Disease progression requiring hospitalization occurred in 4 of 74 patients (5.4%). No deaths were recorded during the 28–day follow-up. Molnupiravir treatment was not associated with a significant reduction in viral load by day 5 of therapy. **Conclusion**. When administered within the first three days after symptom onset, molnupiravir appears to reduce the risk of hospitalization and mortality.
**Keywords**: Antiviral Agents; COVID-19; SARS-CoV-2; Hospitalization; Mortality; Treatment Outcome

**Sažetak**
**Uvod.** Molnupiravir je oralni antivirusni lek koji je odobren za lečenje pacijenata sa lakom i srednjeteškom kliničkom slikom *Severe acute respiratory syndrome coronavirus-2* infekcije. Patofiziološki smanjuje replikaciju virusa. Cilj istraživanja bio je proceniti efikasnost i sigurnost primene molnupiravira. **Materijal i metode**. Retrospektivna analiza koja obuhvata 74 nehospitalizovana pacijenta lečena u Kovid bolnici Univerzitetskog kliničkog centra Vojvodine tokom 2022. godine sa lakom ili srednjeteškom kliničkom slikom. Efikasnost je ispitivana na osnovu broja hospitalizacija ili smrtnog ishoda u toku 28 dana. **Rezultati.** Istraživanje je pokazalo da je samo kod 4/74 (5,4%) došlo do razvoja težeg oblika bolesti i potrebe za hospitalnim lečenjem. Preživljavanje je bilo do 28 dana kod svih pacijenata. Lečenje molnupiravirom nije bilo povezano sa smanjenjem broja virusnih čestica petog dana terapije. **Zaključak.** Ako se primeni u prva tri dana od pojave simptoma molnupiravir smanjuje broj hospitalizacija i smrtnih ishoda.
**Ključne reči:** antivirusni lekovi; COVID-19; SARS-CoV-2; hospitalizacija; mortalitet; ishod lečenja

### Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in approximately 775 million confirmed cases and more than 7 million documented deaths worldwide as of April 2025, according to date published by the World Health Organization (WHO) [1]. In the Republic of Serbia, approximately 2.6 million individuals have been infected, with 18,307 reported deaths [2]. A substantial proportion of patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) required hospitalization, particularly older adults over 65 years of age and those with underlying comorbidities [3]. Given the potential of SARS-CoV-2 to cause severe acute respiratory syndrome and fatal outcomes, the development of effective therapeutic strategies aimed at reducing disease progression, hospitalization, and mortality has been major clinical priority [4].

Molnupiravir is a direct-acting oral antiviral agent that has demonstrated efficacy in reducing SARS-CoV-2 replication and viral RNA levels in the nasopharynx [5,6]. It is generally well tolerated, with a favorable safety profile; however, it is not indicated for use in children or pregnant women [4]. Molnupiravir is a nucleoside analogue that inhibits viral replication of several RNA viruses, including SARS-CoV-2. It inhibits the viral enzymes RNA polymerase and reverses protease. After intracellular conversion to its active triphosphate form, molnupiravir is incorporated into viral RNA in place of cytidine, leading to the accumulation of mutations that ultimately prevent effective viral replication [7,8]. Clinical trials and real-world studies have demonstrated that molnupiravir reduces the risk of severe outcomes in patients with mild to moderate COVID-19 who are at increased risk of disease progression [9]. The drug is administered

✉ Corresponding author: Vedrana Petrić, E-mail: vedrana.petric@mf.uns.ac.rs

***Abbreviations***

SARS-CoV-2 – severe acute respiratory syndrome coronavirus-2
COVID 19 – Corona virus disease
WHO – World Health Organization
MVL – mean viral load
RNA – ribonucleic acid
FDA – Food and Drug Administration
UCCV – University Clinical Center of Vojvodina
GCP – good clinical practice
RT-PCR – reverse transcription polymerase chain reaction
CRP – C-reactive protein
AST – aspartate aminotransferase
ALT – alanine transaminase
GGT – gamma-glutamyltransferase

orally at a dose of 800 mg every 12 hours for five days [10]. According to studies by Mahase and Gentile, molnupiravir administration reduced the risk of hospitalization or death by approximately 50% among non-hospitalized adults with mild to moderate COVID-19 who were at high risk for severe disease [8,10]. By the end of 2021, the research was carried out on 10 million of patients [10]. In the Republic of Serbia, molnupiravir was introduced into clinical practice in early 2022, followed by the approval of another oral antiviral agent, nirmatrelvir/ritonavir, for emergency use by the U.S. Food and Drug Administration (FDA).

The aim of this study was to evaluate the effectiveness and safety of molnupiravir administration.

## Material and Methods

The study was designed as a retrospective observational study involving 74 non-hospitalized patients who were examined and treated on an outpatient basis at the COVID Hospital of the University Clinical Center of Vojvodina (UCCV). Patient enrollment began in early 2022, coinciding with the introduction of molnupiravir into clinical use in Serbia.

The study was approved by the Ethics Committee of UCCV and conducted in accordance with Good Clinical Practice (GCP) guidelines. Data were collected through a review of standard medical documentation and the internal UCCV clinical database.

The inclusion comprised adult patients of both sexes with confirmed SARS-CoV-2 infection, diagnosed by either a rapid antigen test or reverse transcription polymerase chain reaction (RT-PCR) performed in reference laboratories. Patients were required to present within five days of symptom onset and to have a mild to moderate clinical form of COVID-19, as defined by the WHO Clinical Progression Scale **(Table 1)** [11].

Exclusion criteria included age under 18 years, current hospitalization at the time of diagnosis, failure to meet diagnostic criteria for COVID-19, chronic dialysis, pregnancy or breastfeeding, severe neutropenia (absolute neutrophil count < $0.5\times10^9$/L), and thrombocytopenia (platelet count <$100\times10^9$/L).

All patients received molnupiravir at the dose of 800 mg twice per day, in accordance with the national treatment protocol [12].

The following data were recorded for each patient: demographic characteristics, clinical presentation, vital signs, comorbidities, treatment duration, and clinical outcomes. At baseline, all patients underwent routine laboratory testing, including complete blood count with differential, creatinine and urea, electrolytes (sodium, potassium, chloride), bilirubin, C-reactive protein (CRP), D-dimer, and liver function tests (aspartate aminotransferase [AST], alanine transaminase [ALT], and gamma-glutamyltransferase [GGT]). Chest radiography was performed in all patients as part of standard diagnostic evaluation. Pneumonia was diagnosed based on a combination of clinical findings, laboratory results, and radiological evidence.

The effectiveness of molnupiravir was evaluated based on its ability to reduce disease progression, hospitalization, and mortality. Patients were followed for 28 days after treatment initiation. The primary outcome was the incidence of hospitalization for any

**Table 1.** World Health Organization Clinical Progression Scale

| Patient state | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected: no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic: viral RNA detected | 1 |
| | Symptomatic: Independent | 2 |
| | Symptomatic: Assistence needed | 3 |
| Hospitalised: moderate disease | Hospitalised: No oxygen therapy | 4 |
| | Hospitalised: Oxygen by mask or nasal prongs | 5 |
| Hospitalised: severe diseases | Hospitalised: Oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation p02/Fi02 >150 or Sp02/Fi02 >200 | 7 |
| | Mechanical ventilation Sp02/Fi02 < 150 (Sp02/Fi02 <200) or vasopressors | 8 |
| | Mechanical ventilation Sp02/Fi02 < 150 and vasopressors, dialysis or ECMO | 9 |
| Dead | Dead | 10 |

cause or death within 28 days in patients who received at least one dose of molnupiravir and were not hospitalized prior to treatment initiation.

Adverse events were evaluated during the entire treatment period and 14 days after the end of treatment; data on serious adverse events associated with the applied treatment regimen were collected until the end participation in the, up to day 28.

Antiviral activity was assessed by evaluating viral clearance, defined as RT-PCR negativity of nasopharyngeal swabs on day 5 of treatment.

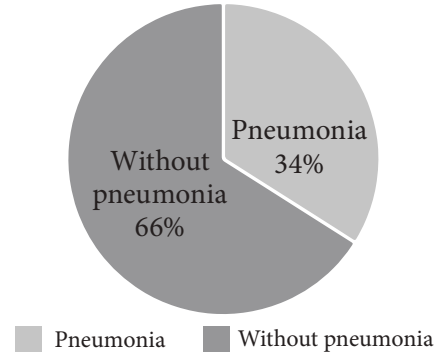
Statistical analysis was performed using IBM SPSS Statistics software, version 20.0.

Categorical variables were analyzed using the $\chi^2$ test or Fisher's exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation for normally distributed data or as median with interquartile range for non-normality distributed data. Given that most variables deviated from normal distribution, nonparametric tests were applied where appropriate. A p-value of <0.05 was considered statistically significant. Results are presented in tables and graphs with accompanying textual interpretation.

## Results

The study population consisted of 74 non-hospitalized patients treated on an outpatient basis at the COVID Hospital of the UCCV who met the inclusion criteria. The mean age was 63.82 ± 23.7 years (range: 23-96). The cohort included an equal number of male and female patients (37/74, (50%) each).

Among patients with confirmed SARS-CoV-2 infection, 62 (83.73%) were vaccinated, while 12 (16.21%) were unvaccinated. The Sinopharm/BBIBP vaccine was the most frequently administered, accounting for 40/62 (67.74%) of vaccinated patients, followed by Pfizer/BioNTech in 16/62 (25.80%), and other vaccines in 6/62, (9.67%). The predominance of the Sinopharm/BBIBP vaccine was statistically significant compared with Pfizer/BioNTech and other vaccines




**Graph 1.** Presence of pneumonia at admission

($\chi^2$ = 10.28; p = 0.001). Comorbidities were common, with 55/74 patients (74.32%) having at least one comorbidity. Cardiovascular diseases and risk factors were the most prevalent, present in 47/55 patients (85.45%), followed by diabetes mellitus in 17/55 (30.95%) and obesity in 17/55 (30.95%).

Molnupiravir therapy was initiated within three days of symptom onset in the majority of patients; only four patients received treatment on the fourth day after symptom onset, in accordance with national treatment guidelines.

At baseline, radiologically confirmed pneumonia was present in 25/74 patients (34%) (**Graph 1).**After five days of treatment with molnupiravir, radiological regression of pneumonia was observed in 8/25 patient (32%), although this finding did not reach statistical significance ($\chi^2$ =3.24; p = 0.07). Four patients experienced disease progression with worsening pneumonia and required hospitalization.

According to the WHO Clinical Progression Scale, 49/74 patients (66%) presented with a mild ambulatory form of disease (score 2), while 25/74 (34%) had a moderate ambulatory form (score 3) at baseline. Disease progressed requiring hospitalization occurred in 4/74 patients (9.45%). Among these, three required oxygen supplementation via face mask (score 5), and one patient required invasive mechanical ventilation (score 7). Survival through day 28 was achieved in all

**Table 2.** Adverse event incidence

| Adverse event | Molnupiravir (N=74) |
|---|---|
| Patients with adverse events | Number (percentage) |
| Adverse event | 22/74 (29.77%) |
| Adverse event related to drug administration | 0 |
| Serious adverse event | 0 |
| Fatal outcome | 0 |
| Nausea | 15/22 (68.18%). |
| Emesis | 3/22 (13.63%) |
| Diarrhea | 3/22 (13.63%) |
| Headache | 1/22 (4.54%) |

**Table 3.** Biochemical parameters of patients

| Biochemical parameter | Initial values (N = 74) | Third day treatment values (N = 74) |
|---|---|---|
| Leukocytes (4.00 - 10.00 x $10^9$/L) | 6.36 (3.34 – 13.55) | 6.14 (3.36-10.06) |
| Lymphocytes (20 - 40%) | 25.12 (10-46) | 29.8 (11-53.2) |
| Neutrophils (50 - 75%) | 64 (39-88) | 62.185 (32.8-80) |
| Erythrocytes (4.2 - 6.00 x $10^{12}$/L) | 4.73 (3.7-6.0) | 4.71 (3.78- 5.97) |
| Hemoglobin (130-170 g/L) | 144 (114-171) | 147 (115-170) |
| Hematocrit (0.400- 0.540 L/L) | 0.452 (0.304 – 0.554) | 0.514 (0.33-0.459) |
| Thrombocytes (140 – 400 x $10^9$/L) | 186 (82- 286) | 202 (90-390) |
| CRP (< 5.0 mg/L) | 20.40 (1-114) | 12.1 (1-193) |
| Urea (2.5 - 7.5 mmol/L) | 5.99 (2.4-11.4) | 6.18 (2.7-15.7) |
| Creatinine (64 - 111 mmol/L) | 83.08 (54-139) | 83.23 (59-117) |
| Na (136 – 145 mmol/L) | 140.12 (134-145) | 140.49 (135-147) |
| K (3.5 – 5.5 mmol/L) | 4.01 (3.3-5.2) | 4.10 (3.5-5.6) |
| Cl (98– 107 mmol/L) | 102.29 (94-109) | 102.82 (95-109) |
| AST (5-34 U/L) | 29.97 (12-67) | 30.43 (15-59) |
| ALT (5-55 U/L) | 34.67 (9-83) | 34.32 (11-80) |
| GGT (11-59 U/L) | 37.39 (8-98) | 37.36 (8-86) |
| D dimer (< 0.5 mg/L FEU) | 0.59 (0.22-2.45) | 0.56 (0.2-3.06) |
| Procalcitonin (0.00 - 0.05 ng/mL) | 0.05 (0.05) | 0.556 (0.05-5.64) |

CRP – C-reactive protein, Na - Sodium, K – Potassium, Cl – Chloride, AST – Aspartate aminotransferase, ALT – Alanine transaminase, GGT – Gamma-glutamyltransferase

patients, including those who discontinued outpatient follow-up and those who required hospitalization.

Adverse events were reported in 22/74 patients (29.77%). The most frequently observed adverse event was nausea, reported by 15/22 patients (68.18%). No serious adverse events related to molnupiravir treatment were recorded **(Table 2).**

Laboratory parameters measured at baseline and on day 3 of treatment are presented in **Table 3**. Overall, biochemical and hematological values remained without reference ranges, with no clinically relevant or statistically significant changes observed during treatment.

Clinical improvement, defined as symptom resolution or marked symptom reduction, was observed in the majority of patients. Complete symptom resolution by day 5 occurred in 49/74 patients. In the remaining non-hospitalized patients, gradual clinical improvement was documented between days 5 and 10. No deaths were recorded during the 28-day follow-up period.

At baseline, RT-PCR testing for SARS-CoV-2 was performed in 22/74 (29.77%) patients, while the remaining patients were diagnosed using rapid antigen test. Follow-up RT-PCR testing on day 5 was available for 42/74 patients (56.75%). Among those tested, 29/42 patients (69.04%) remained RT-PCR positive on day 5. Based on these findings, molnupiravir treatment in this cohort was not associated with a reduction in mean viral load (MVL) by day 5 of therapy.

## Discussion

The study evaluated the effectiveness and safety of molnupiravir in 74 non-hospitalized patients with mild to moderate SARS-CoV-2 infection treated on an outpatient basis at the COVID Hospital Mišeluk, UCCV. The mean patient age was 63.82 ± 23.7 years, with an equal sex distribution, consistent with demographic characteristics reported in other real-world studies evaluating antiviral therapy in high-risk populations [4,13].

Although sex-related differences were not a primary focus of this study, a large study conducted in the USA, involving 308,010 hospitalized patients, demonstrated worse outcomes among male patients, including respiratory failure, mortality, and longer hospital stays [14]. The underlying mechanisms are likely multifactorial, with hormonal influences – particularly the immunomodulatory effects of estrogens – proposed as one contributing factor [15].

The study population consisted of patients at increased risk for disease progression due to age and comorbidities. Overall, 74.32% of patients had at least one comorbidity, with cardiovascular diseases – primarily hypertension – being the most prevalent. This finding aligns with previous reports identifying hypertension, obesity, diabetes mellitus, chronic kidney disease, asthma, and autoimmune disorders as major risk factors for severe COVID-19 [16]. Notably, even among patients without documented comorbidities

(19/74), 10 were older than 60 years, and 9 were over 45, supporting the decision to initiate antiviral therapy in this subgroup, in line with the existing evidence indicating increased hospitalization rates among individuals aged ≥45 years [16].

Most patients involved in the study were vaccinated (62/74, (83.73%)), with predominance of the Sinopharm/BBIBP vaccine administered to 40/62 patients (67.74%). Before the appearance of the Omicron variant of the virus, no studies were conducted involving unvaccinated patients [17]. In the Republic of Serbia, vaccination started in late 2020, and 47.1% of the population were fully vaccinated (3 doses) by the time of this study, according to data from the Institute of Public Health "Dr Milan Jovanović Batut" [1].

According to the national protocol, molnupiravir was administered within three days of symptom onset in the majority of patients, with the exception of four individuals who later required hospitalization and received the drug on the fourth day after symptom onset. Results from a phase III randomized, double-blind clinical trial demonstrated that molnupiravir administration within five days of symptom onset significantly reduced the risk of hospitalization from any cause or death by day 29, which is consistent with our findings [4]. Notably, in our study, patients who progressed to more severe disease received treatment later than those who remained ambulatory, underscoring the importance of early antiviral initiation. These observations support the concept that administering molnupiravir as close as possible to symptom onset may reduce the risk of disease progression.

SARS-CoV-2 infection is known to induce systemic inflammation and immune dysregulation, affecting multiple organ systems [18]. Bilateral pneumonia remains the most common and clinically significant complication. Approximately 15–20% of patients develop severe pneumonia requiring hospitalization and oxygen therapy, while about 5% require mechanical ventilation [19]. In our cohort, 25/74 (34%) patients presented with pneumonia at baseline. After five days of molnupiravir therapy, radiological regression of pneumonia was observed in 8/25 (32%) patients, although this finding did not reach statistical significance ($p = 0.28$). Overall, 5.4% of patients progressed to a more severe form of pneumonia requiring hospitalization and oxygen therapy, and only one patient (1.34%) required mechanical ventilation. These proportions are lower than those reported in populations not treated with antiviral therapy [5,20].

Molnupiravir was generally well tolerated. The most frequently reported adverse effects – nausea, vomiting, diarrhea, and headache – are consistent with previously published data [5]. In our study, nausea was the most common adverse event, reported in 15/22 (68.18%) patients. No serious adverse events were observed, and treatment discontinuation was not required in any patient. Furthermore, no clinically significant changes in laboratory parameters were detected at baseline or on the third day of therapy.

Recent studies further support the potential role of molnupiravir in preventing disease progression in high-risk patients. Gentile et al. demonstrated its effectiveness in reducing progression to severe disease [8], while a Czech study by Pavlik et al. reported reduced mortality with early antiviral administration [21]. Additionally, a large national study including 1,172 patients showed that only four required hospitalization, with Gmizić et al. reporting a 97.9% reduction in hospitalization risk associated with molnupiravir use [22]. Conversely, some studies have yielded neutral results; for example, Yip et al. found no statistically significant difference in hospitalization risk between treated and untreated patients [23]. In our cohort, only four patients required hospitalization, and no fatal outcomes occurred during the 28-day follow-up period.

While a meta-analysis reported a high proportion of patients achieving viral RNA negativity by day 5 [24], and Butler et al. demonstrated shorter recovery times with molnupiravir treatment [25], our findings did not show a significant reduction in viral load by day 5. Among 42 patients who underwent follow-up PCR testing, 29 (69.04%) remained PCR-positive [27,28]. Nevertheless, according to the WHO Clinical Progression Scale, most patients experienced clinical improvement, with complete symptom resolution by day 5 observed in 49/74 cases [11].

Sinha et al. reported a significantly higher rate of clinical improvement in patients receiving molnupiravir compared to placebo (80.8% vs. 32.1%) [26], suggesting that molnupiravir reduces viral load more rapidly than placebo, potentially decreasing SARS-CoV-2 transmissibility.

## Conclusion

Molnupiravir represents a valuable therapeutic option for the early outpatient treatment of COVID-19 in patients at increased risk of disease progression. In this real-world cohort, early administration was associated with a low rate of hospitalization, absence of fatal outcomes, and a favorable safety profile. These findings support the role of molnupiravir as part of the therapeutic arsenal against COVID-19.

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Rad je primljen 28. XI 2025.
Recenziran 2. II 2026.
Prihvaćen za štampu 2. II 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:251-256.

Med Pregl 2025; LXXVIII (9-12): 257-263. Novi Sad: septembar-decembar.

# EFFICACY OF PREOPERATIVE PREGABALIN IN ACUTE POST-THORACOTOMY PAIN

# *EFIKASNOST PREOPERATIVNOG PREGABALINA KOD AKUTNOG BOLA NAKON TORAKOTOMIJE*

**Stanislava PETROVIĆ[1], Siniša MAKSIMOVIĆ[1,2], Ivana SPASOJEVIĆ[1], Jelena ISAKOVIĆ[2] and Borislav TAPAVIČKI[2]**

ORCID NUMBER
Stanislava Petrović – 0009-0000-9742-8350
Siniša Maksimović – 0000-0001-6972-9228
Ivana Spasojević – 0009-0007-1978-5169
Jelena Isaković – 0009-0007-2461-7506
Borislav Tapavički – 0000-0001-8056-4989

Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica[1]
University of Novi Sad, Faculty of Medicine Novi Sad[2]

Original study
*Originalni naučni rad*
UDK 616.24-089.5:616.8-009.7
https://doi.org/10.2298/MPNS2512257P

**Abstract**

**Introduction.** Acute post-thoracotomy pain remains a significant clinical challenge, potentially impairing recovery, increasing opioid consumption, and contributing to the development of chronic post-thoracotomy pain. Pregabalin is increasingly incorporated into multimodal perioperative analgesic protocols; however, the optimal timing of its administration remains uncertain. **Material and Methods.** This prospective, randomized, double-blind study included 40 patients undergoing elective thoracotomy for lung surgery. Patients were randomly allocated using a sealed-envelope method into two groups. Group A received pregabalin 150 mg orally the evening before surgery and 2 hours preoperatively. Group B received pregabalin 75 mg orally the evening before surgery and 2 hours preoperatively, followed by an additional 150 mg postoperative dose on the day of surgery. Postoperative pain intensity was assessed using the Numerical Rating Scale over 48 hours. Total opioid consumption, sedation scores, and adverse effects were also recorded. **Results.** Demographic and perioperative characteristics were comparable between groups. During the first 24 postoperative hours, pain scores and cumulative opioid consumption did not differ significantly. On postoperative day one, Group B demonstrated significantly lower pain scores at 36 hours ($p = 0.035$) and borderline statistical significance at 48 hours ($p = 0.061$). There were no statistically significant differences in total opioid requirements, sedation scores, or incidence of adverse effects between groups. **Conclusion.** Perioperative pregabalin administration including an additional postoperative dose provides superior analgesia during the first postoperative day compared with preoperative administration alone, without increasing opioid consumption or sedation. These findings suggest that dosing timing plays an important role in optimizing acute post-thoracotomy pain management.

**Key words:** Thoracotomy; Pregabalin; Analgesics; Postoperative Pain; Acute Pain; Pain Measurement; Perioperative Care

**Sažetak**

**Uvod.** Akutni posttorakotomijski bol predstavlja značajan klinički problem, koji može usporiti postoperativni oporavak, povećati potrošnju opioida i doprineti razvoju hroničnog bola. Pregabalin se sve češće primenjuje kao deo multimodalne perioperativne analgezije, ali optimalno vreme njegove primene još uvek nije jasno definisano. **Materijal i metode.** Ova prospektivna, dvostruko slepa studija obuhvatila je 40 pacijenata podvrgnutih elektivnoj torakotomiji zbog hirurškog lečenja plućnih oboljenja. Pacijenti su naizmenično raspoređivani u dve grupe. Grupa A je primala pregabalin u dozi od 150 mg per os veče pre operacije i dva sata pre operacije. Grupa B je primala pregabalin u dozi od 75 mg u istim vremenskim intervalima, uz dodatnu postoperativnu dozu od 150 mg na dan operacije. Intenzitet postoperativnog bola procenjivan je *Numeričkom skalom bola* tokom 48 sati. Takođe su praćeni potrošnja opioida, stepen sedacije i pojava neželjenih efekata. **Rezultati.** Nije uočena statistički značajna razlika između grupa u pogledu demografskih i perioperativnih karakteristika. Tokom prva 24 sata nakon operacije, vrednosti skora bola i kumulativna potrošnja opioida bile su uporedive. Tokom prvog postoperativnog dana, pacijenti u grupi B imali su statistički značajno niži skor bola u 36. satu ($p = 0,035$), kao i granično statistički značajnu razliku u 48. satu ($p = 0,061$). Potrošnja opioida, stepen sedacije i učestalost neželjenih efekata nisu se razlikovali između grupa. **Zaključak.** Perioperativna primena pregabalina uz dodatnu postoperativnu dozu obezbeđuje bolju analgeziju tokom prvog postoperativnog dana u poređenju sa isključivo preoperativnom primenom, bez povećanja potrošnje opioida ili sedacije, što ukazuje na značaj vremena primene u lečenju akutnog posttorakotomijskog bola.

**Ključne reči**: torakotomija; pregabalin; analgetici; postoperativni bol; akutni bol; procena bola; perioperativna nega

## Introduction

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is inherently subjective and multidimensional, influenced by physiological and psychological factors, as well as prior experiences, cultural background, fear, and anxiety. In a broader clinical context, "pain is everything the patient says it hurts" [1]. Effective perioperative analgesia and attenuation of the surgical stress response are essential for improving postoperative outcomes and accelerating recovery. Early control of postoperative pain

✉ Corresponding author: Stanislava Petrović, E-mail: stasapetrovic@yahoo.com, sinisa.maksimovic@mf.uns.ac.rs

***Abbreviations***

VAS – Visual Analogue Scale
CSF – cerebrospinal fluid
ASA – American Society of Anesthesiologists
BMI – body mass index
NSAIDs – non-steroidal anti-inflammatory drugs
NRS – numerical rating sscale
POSS – Pasero Opioid-Induced Sedation Scale

not only enhances patient comfort and confidence but also reduces the risk of central sensitization and wind-up phenomena [2]. Acute post-thoracotomy pain is multifactorial. Contributing factors include skin incision, soft tissue trauma, rib retraction, rib resection or fracture, costovertebral joint dislocation, and the intercostal nerve injury. Additional nociceptor activation results from pleural irritation caused by surgical manipulation, chest tube placement, and pleural effusion. Intercostal nerve injury is considered the principal mechanism, occurring either through direct mechanical trauma from rib retractors or rib resection, or indirectly through sustained traction leading to ischemic nerve damage. Pain may also arise from nerve entrapment within scar tissue or improper rib healing. Afferent sensory transmission from thoracic dermatomes (C3-T10) travels via the intercostal, vagal, and phrenic nerves [3]. Gabapentinoids are widely used for the management of neuropathic pain conditions, including postherpetic neuralgia and as adjunctive therapy in epilepsy. Pregabalinis additionally indicated for fibromyalgia and neuropathic pain associated with diabetes mellitus and spinal cord injury. Evidence from multiple clinical trials suggests that perioperative gabapentinoid administration may reduce early postoperative pain intensity and opioid consumption [4]. Gabapentinoids are structural analogues of γ-aminobutyric acid. By binding to the α-2δ subunit of presynaptic voltage-gated calcium channels, they reduce calcium influx and inhibit the release of excitatory neurotransmitters involved in nociceptive transmission, thereby attenuating central sensitization [5]. Additional antinociceptive effects may involve activation of descending noradrenergic inhibitory pathways within the brain and spinal cord [6].

Key pharmacokinetic differences between gabapentin and pregabalin primarily relate to bioavailability. Pregabalin is absorbed throughout the small intestine and exhibits linear pharmacokinetics without saturation at therapeutic concentrations, whereas gabapentin demonstrates dose-dependent absorption [7,8]. The elimination of half-life of gabapentin ranges from 4.8 to 8.7 hours, while pregabalin has a half-life of approximately 5.5 to 6.3 hours [5]. Both agents require dose adjustment in renal impairment [9,10]. Gabapentinoids are generally well tolerated. The most frequently reported adverse effects of pregabalin include dizziness, headache, sedation, visual disturbances, and peripheral edema [11,12]. Even in cases of overdose, management is typically supportive [13–15]. Reduced perioperative opioid requirements associated with gabapentin use may decrease the incidence of opioid-related adverse effects, including postoperative delirium and vomiting [11,16].

Patients who received gabapentin either prior to surgery or immediately after surgical incision demonstrated consistently lower Visual Analogue Scale (VAS) pain scores at all assessed time points and required less fentanyl compared with placebo [17,18]. Regarding Pregabalin, its efficacy in combination with ibuprofen was evaluated in patients undergoing third molar extraction. Participants were divided in groups: placebo, pregabalin 75 mg and pregabalin 150 mg. Pain intensity was assessed for six postoperative days, and patients premedicated with 150 mg pregabalin reported significantly lower numerical pain scores compared with other groups [19]. Similarly, a study compared preoperative gabapentin alone versus combined preoperative and postoperative gabapentin administration in patients undergoing total knee arthroplasty found that those receiving postoperative gabapentin consumed less morphine via patient-controlled analgesia at 24, 36, and 48 hours. In addition, they demonstrated improved active knee flexion on the second and third postoperative days compared with patients who received only preoperative gabapentin [20]. Moreover, a Cochrane review that included data from four unpublished trials concluded that gabapentin is effective in the treatment of established acute postoperative pain, even when administered exclusively after surgery [21].

Pharmacokinetic data indicate that peak plasma concentrations occur approximately 2 hours after gabapentin administration and 1 hour after pregabalin administration. However, peak cerebrospinal fluid (CSF) concentrations may occur considerably later. For pregabalin, CSF peak levels have been reported up to 8 hours post-administration, suggesting that earlier dosing may enhance pre-emptive analgesic effects [22].

Several investigations have attempted to determine the optimal perioperative dosing of gabapentinoids. For both gabapentin and pregabalin, lower doses have generally been associated with insufficient analgesic efficacy [23]. Although gabapentinoids are included in recommended Prospect Working Group, clear guidance regarding optimal dosing strategies and the need for repeated preoperative administration remains lacking [24]. Furthermore, two studies demonstrated that pregabalin at a dose of 150 mg – but not 75 mg – was superior to placebo in reducing postoperative opioid consumption or pain intensity [25,26].

With respect to drug selection, definitive conclusions regarding the comparative efficacy of gabapentin and pregabalin in the management of acute postoperative pain remain limited due to insufficient and inconclusive evidence [27]. Although both agents have been investigated in thoracic surgery, no study to date has directly compared two gabapentinoids in this setting [28,29]. Pharmacokinetic considerations may further influence clinical effectiveness. Pregabalin reaches peak cerebrospinal fluid concentrations approximately eight hours after administration, whereas gabapentin requires approximately 4–6 hours to achieve similar levels. Therefore, administration the evening before surgery may theoretically provide greater pre-emptive analgesic benefit than dosing two hours preoperatively. However, earlier initiation may also increase the risk of dose-related adverse effects, including dizziness, sedation, and confusion [30].

Accordingly, the present study was designed to determine whether preoperative administration of pregabalin (150 mg 12 hours before surgery) or a perioperative regiment (75 mg 12 hours before surgery and 150 mg postoperatively) provides superior control of acute post-thoracotomy pain.

## Material and Methods

This prospective, double-blind study included patients undergoing elective thoracotomy at the Clinic for Chest Surgery of the Institute of Pulmonary Diseases of Vojvodina in Sremska Kamenica. The study protocol was approved by the institutional Ethics Committee and Expert Council. Inclusion criteria: age ≥ 18 years, elective thoracotomy for lung disease, American Society of Anesthesiologists (ASA) physical status I-III. Exclusion criteria: known hypersensitivity to pregabalin, pre-existing acute or chronic, age > 70 years, body mass index (BMI) > 30 kg/m$^2$, neurological diseases, use of calcium channel blockers, analgesics, anxiolytics, sedatives, or antidepressants, and opioid or alcohol dependence.

Between January and June 2024, 52 eligible patients were screened. Two declined participation, and ten were excluded due to conversion of surgery to mediastinoscopy for advanced malignant disease. A total of 40 patients were enrolled.

Patients provided written informed consent after receiving detailed oral and written explanations regarding the study objectives, preoperative medication, and anesthetic management. Patients were alternately allocated, according to admission order, into two groups: Group A: Pregabalin 150 mg orally the evening before surgery and 2 hours preoperatively, and Group B: Pregabalin 75 mg orally the evening before surgery and 2 hours preoperatively, followed by 150 mg on postoperative day 0.

Premedication consisted of atropine 0.5 mg. General balanced anesthesia was induced and maintained with propofol, fentanyl, rocuronium and sevoflurane. Patients were intubated using a double-lumen tube. Mechanical ventilation was provided with a mixture of air and oxygen. Standard ASA monitoring was applied in all cases. Hemodynamic parameters were maintained within ± 30% of baseline values. Morphine was administered intravenously at a dose of 0.2 mg/kg approximately one hour before emergence from anesthesia.

Postoperative analgesia included morphine 0.1 mg/kg every 6 hours and Ketorolac 30 mg every 8 hours. For breakthrough pain (VAS > 5), patients received paracetamol 1 g IV, and if inadequate response persisted, morphine 2 mg IV every 10 minutes until analgesia was achieved.

Postoperative pain intensity was assessed using the Numerical Rating Scale (NRS) at 1, 4, 8, 12, 16, 20, and 24 hours postoperatively, and every 6 hours during the second 24-hour period. Cumulative opioid consumption was recorded. Sedation was evaluated using the Pasero Opioid-Induced Sedation Scale (POSS). Adverse effects monitored included nausea, vomiting, dizziness, headache, urinary retention, and visual disturbances.

Descriptive statistics included the mean, standard deviation, and relative frequencies. Inferential analysis was performed using the independent samples t-test, Mann-Whitney U test, or $\chi^2$ test, depending on data type and distribution. Statistical significance was defined as $p < 0.05$.

## Results

Patient characteristics are presented in **Table 1**. Group A included 20 patients with a mean age of 59.00 ± 7.77 years, while group B included 20 patients with a mean age of 60.70 ± 10.19 years (p = 0.557). The mean body weight was 75.30 ± 11.74 kg in Group A 75.05 ± 10.71 kg in Group B, with no statistically significant difference between groups (p = 0.944).

No statistically significant differences were observed between groups regarding sex distribution (p = 0.752), ASA physical status (p = 1.00), side of thoracotomy (p = 0.091), or type of surgical procedure (p = 0.857). Intraoperative fentanyl and morphine requirements were compatible between groups **(Table 2).** There were no statistically significant differences in cumulative morphine or paracetamol consumption during the first 48 postoperative hours. Analysis of NRS pain scores during the zero postoperative day **(Table 3)** demonstrated no statistically significant difference between groups at any measured time point. Similarly, no statistically sig-

**Table 1.** Patient characteristics by group

| | Group | | | | p value |
|---|---|---|---|---|---|
| | A (N=20) | | B (N=20) | | |
| | N | % | N | % | |
| Sex (male/female) | 11/9 | 55/45 | 10/10 | 50/50 | 0.752 |
| ASA I | 1 | 5 | 1 | 5 | |
| ASA II | 15 | 75 | 15 | 75 | 1.00 |
| ASA III | 4 | 20 | 4 | 20 | |
| Thoracotomy (right/left) | 16/4 | 80/20 | 11/9 | 55/45 | 0.091 |
| Type of operation | | | | | |
| Atypical resection of upper lung lobe | 5 | 25 | 5 | 25 | |
| Atypical resection of lower lung lobe | 1 | 5 | 1 | 5 | |
| Upper lung lobectomy | 7 | 35 | 6 | 30 | 0.857 |
| Lower lung lobectomy | 2 | 10 | 4 | 20 | |
| Lower lung bilobectomy | 3 | 15 | 1 | 5 | |
| Pneumonectomy | 2 | 10 | 3 | 15 | |

**Table 2.** Fentanyl and Morphine administered during surgery

| | Group | N | Mean value | Standard deviation | p value |
|---|---|---|---|---|---|
| Fentanyl (mcg) | A | 20 | 373.7500 | 108.05548 | 0.763 |
| | B | 20 | 362.5000 | 125.52521 | |
| Fentanyl (mcg/kg) | A | 20 | 5.0490 | 1.51833 | 0.671 |
| | B | 20 | 4.8350 | 1.63588 | |
| Morphine (mg) | A | 20 | 6.9500 | 2.21181 | 0.227 |
| | B | 20 | 6.0500 | 2.41650 | |
| Morphine (mg/kg) | A | 20 | 0.1277 | 0.14987 | 0.170 |
| | B | 20 | 0.0799 | 0.03038 | |

**Table 3.** NRS scale mean values on postoperative day 0

| | Group | | | | | | | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | A | | | | B | | | | |
| | Mean value | Minimum | Maximum | SD | Mean value | Minimum | Maximum | SD | |
| NRS 0 h | 2.50 | 0.00 | 7.00 | 1.54 | 3.55 | 0.00 | 9.00 | 2.58 | 0.127 |
| NRS 1 h | 3.85 | 0.00 | 8.00 | 2.32 | 4.90 | 0.00 | 9.00 | 2.10 | 0.142 |
| NRS 4 h | 3.85 | 0.00 | 8.00 | 1.90 | 3.35 | 1.00 | 6.00 | 1.23 | 0.329 |
| NRS 8 h | 3.00 | 0.00 | 6.00 | 1.41 | 2.75 | 0.00 | 6.00 | 1.48 | 0.588 |
| NRS12 h | 2.75 | 0.00 | 7.00 | 1.48 | 2.35 | 0.00 | 4.00 | 1.18 | 0.351 |
| NRS16 h | 2.20 | 0.00 | 5.00 | 1.20 | 2.15 | 0.00 | 6.00 | 1.39 | 0.903 |
| NRS20 h | 2.35 | 0.00 | 6.00 | 1.50 | 1.60 | 0.00 | 5.00 | 1.43 | 0.113 |
| NRS24 h | 2.50 | 0.00 | 5.00 | 1.43 | 2.25 | 0.00 | 6.00 | 1.55 | 0.600 |

**Table 4.** Differences in the sedation scale mean values between groups during postoperative day 0

| | Group | | | | | | | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | A | | | | B | | | | |
| | Mean value | Minimum | Maximum | SD | Mean value | Minimum | Maximum | SD | |
| POSS 1 h | 1.55 | 0.00 | 3.00 | 0.94 | 1.60 | 0.00 | 3.00 | 0.68 | 0.884 |
| POSS 4 h | 1.25 | 0.00 | 3.00 | 0.97 | 1.15 | 0.00 | 2.00 | 0.75 | 0.808 |
| POSS 8 h | 1.00 | 0.00 | 3.00 | 0.92 | .75 | 0.00 | 2.00 | 0.72 | 0.418 |
| POSS 12 h | 095 | 0.00 | 3.00 | 0.89 | 0.70 | 0.00 | 2.00 | 0.73 | 0.391 |
| POSS 16 h | 0.90 | 0.00 | 3.00 | 0.79 | 0.70 | 0.00 | 2.00 | 0.66 | 0.453 |
| POSS 20 h | 0.40 | 0.00 | 2.00 | 0.60 | 0.25 | 0.00 | 2.00 | 0.55 | 0.323 |
| POSS 24 h | 0.10 | 0.00 | 1.00 | 0.31 | 0.20 | 0.00 | 2.00 | 0.52 | 0.604 |

**Table 5.** Differences in the NRS scale average values between the groups during postoperative day 1

| | Group | | | | | | | | p |
|---|---|---|---|---|---|---|---|---|---|
| | A | | | | B | | | | |
| | Mean value | Minimum | Maximum | Standard deviation | Mean value | Minimum | Maximum | Standard deviation | |
| NRS 30 h | 2.70 | 0.00 | 6.00 | 1.45 | 1.95 | 0.00 | 4.00 | 1.32 | 0.096 |
| NRS 36 h | 2.15 | 0.00 | 5.00 | 1.23 | 1.35 | 0.00 | 3.00 | 1.09 | 0.035 |
| NRS 42 h | 2.05 | 0.00 | 5.00 | 1.28 | 1.50 | 0.00 | 4.00 | 1.15 | 0.160 |
| NRS 48 h | 1.60 | 0.00 | 4.00 | 1.05 | 1.00 | 0.00 | 3.00 | 0.92 | 0.061 |

nificant differences were observed in sedation scores during the same period **(Table 4)**. With regard to adverse effects (nausea, dizziness, postoperative headache, urine retention, blurred vision), only one patient in each group reported dizziness. On the first postoperative day (**Table 5),** Group B demonstrated lower mean NRS scores compared with Group A at 36 hours (p = 0.035), which was statistically significant. At 48 hours, pain scores were also lower in Group B, reaching borderline statistical significance (p = 0.061).

## Discussion

Pregabalin has previously been evaluated in thoracic surgery. Studies have shown that pregabalin 75 mg twice daily significantly enhances the analgesic efficacy of self-administered NSAIDs compared with multimodal continuous epidural analgesia in acute post-thoracotomy pain. Additionally, postoperative administration of 150 mg pregabalin combined with continuous epidural analgesia significantly reduced post-thoracotomy shoulder pain [31,32]. The present study aimed to determine whether preoperative administration alone (150 mg before surgery) or a perioperative regimen (75 mg before and after surgery) provides superior control of acute post-thoracotomy pain. Our findings indicate that continuation of pregabalin 75 mg with a single postoperative dose resulted in significantly better analgesia on the first postoperative day, without increasing opioid consumption or sedation.

Hill et al. reported that pregabalin 300 mg following dental surgery prolonged analgesia but was associated with a higher incidence of adverse events [33]. Even lower doses, such as 100 mg, have been associated with clinically significant dizziness and sedation in outpatient settings [34]. For this reason, considering concomitant postoperative morphine use – which shares a similar adverse-effect profile – this study evaluated lower pregabalin doses (75 mg and 150 mg) to balance efficacy and safety.

Gabapentin has been more extensively studied in acute postoperative pain and has consistently demonstrated reductions in pain intensity, opioid consumption, and opioid-related adverse effects [35]. In contrast, evidence regarding pregabalin remains inconsistent, likely due to heterogeneity in dosing regimens, timing of administration, surgical procedures, and multimodal analgesic protocols [36].

Some studies have shown no significant benefit from a single 100 mg preoperative pregabalin dose in minor gynecological surgery, with increased adverse effects observed within 24 hours [37]. White et al. demonstrated that pregabalin doses ranging from 75 mg to 300 mg did not reduce either preoperative anxiety or postoperative pain [38]. Other investigations demonstrated that doses between 150-300 mg significantly reduced postoperative pain and opioid consumption following total joint arthroplasty, with improved mobility by the third postoperative day, and acceptable safety profile and tolerability [39]. Similarly, a multimodal analgesic regimen consisting of pregabalin and diclofenac has been shown to reduce both resting pain intensity and pain on movement following hysterectomy. Comparative evaluation of different pregabalin dosages (75 mg, 150 mg, and 300 mg) and their associated adverse effects suggests that pre-emptive oral administration of 150 mg pregabalin provides the most favorable analgesic profile with least side effects [40]. A similar regimen has also demonstrated reductions in morphine consumption and postoperative pain following laparoscopic sleeve gastrectomy [41].

The present study specifically evaluated the timing and potential pre-emptive effect of pregabalin in thoracotomy. Given its half-life of approximately 6.5 hours, a single preoperative dose would be expected to cover the peak postoperative pain [42]. Any sustained analgesic benefit beyond this window might suggest a pre-emptive mechanism. However, in the present study, preoperative pregabalin alone did not improve analgesia nor prolong its duration, thereby questioning the clinical relevance of a purely pre-emptive strategy in post-thoracotomy pain. Statistically significant differences in pain intensity were observed only on the first postoperative day, with lower pain scores in the group that received an additional postoperative dos-

This study has several potential limitations. First, the administered pregabalin dose may have been insufficient to achieve a stronger analgesic effect. Nevertheless, doses below 300 mg have demonstrated efficacy in other surgical settings [11]. Evidence indicates that preoperative administration of 150 mg pregabalin improves analgesia following procedures such as mastectomy. Importantly, lower doses may reduce the incidence of adverse effects, particularly sedation, which is of special concern in thoracic surgery due to the potential risk of postoperative pulmonary complications [43]. Therefore, investigating lower pregabalin doses for acute post-thoracotomy pain management represents a clinically justified approach.

Second, the study was conducted with a multimodal analgesic framework. The concomitant use of opioid analgesics may have masked early differences between groups during the first 24 postoperative hours and potentially increased the risk of additive adverse effects. A plausible explanation to this effect is that analgesic effects of intraoperative opioids diminished after 24 hours, whereas the maintained pregabalin concentration in Group B contributed to improved analgesia at 36 hours and beyond. Future studies incorporating epidural analgesia – the gold standard for thoracotomy pain management – may yield more definitive conclusions.

Third, a relatively small sample size likely contributed to the borderline statistical significance observed across the entire first postoperative day. Larger randomized trials are required to confirm these findings. Additionally, long-term outcomes, including the development of post-thoracotomy pain syndrome, were not assessed. Further research should explore whether sustained perioperative pregabalin administration influences chronic pain development. Finally, contemporary literature distinguished between pre-emptive analgesia – aimed to prevent central sensitization before surgical incision – and preventive analgesia, which emphasizes maintaining effective perioperative drug concentration. The findings of this study suggest that maintaining stable pregabalin plasma levels (Group B) may be more clinically relevant than achieving a high preoperative peak concentration alone (Group A).

## Conclusion

Preoperative administration of pregabalin 75 mg (first dose in the evening and second dose 2 hours before surgery), followed by a single 150 mg postoperatively, provided superior analgesia on the first postoperative day compared with a regimen of 150 mg pregabalin administered exclusively preoperatively (evening and 2 hours before surgery). However, opioid consumption and the degree of sedation were comparable between the two groups. These findings support the use of the combined pre- and postoperative pregabalin regimen for the management of post-thoracotomy pain.

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Rad je primljen 22. I 2026.
Recenziran 22. II 2026.
Prihvaćen za štampu 22. II 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:257-263.

Med Pregl 2025; LXXVIII (9-12): 265-269. Novi Sad: septembar-decembar.

REVIEW ARTICLES
*PREGLEDNI ČLANCI*

# MINIMALLY INVASIVE AND NON-INVASIVE TREATMENT OF BENIGN THYROID NODULES

# *MINIMALNO INVAZIVNO I NEINVAZIVNO LEČENJE BENIGNIH ČVOROVA ŠTITASTE ŽLEZDE*

**Radoslav PEJIN[1,2], Tijana IČIN[1,2], Ivana BAJKIN[1,2], Nikolina VUKOVIĆ[1,2], Teodor GRBIĆ[2] and Stefan DRAGIČEVIĆ[3]**

ORCID NUMBER
Radoslav Pejin – 0000-0002-8869-796X
Tijana Ičin – 0000-0002-3886-6518
Ivana Bajkin – 0000-0003-4221-1730
Nikolina Vuković – 0009-0001-8892-4325
Teodor Grbić – 0009-0000-6799-9785
Stefan Dragičević – 0009-0001-0784-704X

University of Novi Sad, Faculty of Medicine Novi Sad[1]
University Clinical Center of Vojvodina, Novi Sad
Clinic of Endocrinology, Diabetes and Metabolic Disorders[2]
Public Health Institution "Holy Apostle Luke" Hospital Doboj, Bosnia and Herzegovina[3]

Review article
*Pregledni članak*
UDK 616.441-08
https://doi.org/10.2298/MPNS2512265P

**Abstract**

**Introduction.** The thyroid gland is a bilobed endocrine organ connected by a thin isthmus and may also present with a pyramidal lobe. **A thyroid nodule** is defined as a localized structural alternation of the thyroid tissue. **Laser thermal ablation** represents a novel minimally invasive intervention, with contemporary guidelines and evidence from randomized trials, observational studies, and multicenter retrospective analyses consistently demonstrating its safety and clinical efficacy in the treatment of symptomatic cold thyroid nodules. **Radiofrequency ablation** is increasingly employed in the management of papillary thyroid microcarcinoma and offers a valuable alternative for patients with medullary thyroid carcinoma who are not suitable surgical candidates. It is also particularly effective in treating recurrent cystic nodules following ethanol ablation and clinically significant lesions with large residual non-cystic components. **Microwave ablation** is a newer technique that has shown substantial improvements in symptom relief and in cosmetic outcomes while preserving thyroid function; however, it has been associated with a relatively higher rate of procedure-related complications. **High-intensity focused ultrasound** is with a non-invasive, computer-guided technique that enables precise targeting while preserving surrounding thyroid tissue. Owing to its lower overall efficacy, higher cost, and limited scientific validation, interventionist use should be restricted to carefully selected patients who are not eligible for other treatment options. For benign thyroid nodules with a significant cystic component, particularly recurrent or symptomatic lesions, current guidelines recommend **percutaneous ethanol injection** as the preferred treatment. **Conclusion**. Whereas surgical intervention was historically the standard approach for thyroid nodules, advances in minimally invasive techniques now provide effective, thyroid-preserving alternatives for appropriately selected patients.

**Key words:** Thyroid Nodule; Minimally Invasive Surgical Procedures; Ablation Techniques; Laser Therapy; Ethanol; High-Intensity Focused Ultrasound Ablation; Microwaves; Radiofrequency Ablation

**Sažetak**

**Uvod.** Štitasta žlezda je endokrini organ leptirastog oblika sačinjen od dva režnja spojena istmusom u blizini kog se nalazi nestalni piramidalni režanj. **Tiroidni nodus** predstavlja lokalizovanu promenu arhitektonike tkiva štitaste žlezde, koja se razlikuje od okolnog žlezdanog parenhima. **Laserska termalna ablacija** je nova minimalno invazivna tehnika. Novi vodiči kao i brojne nerandomizovane, randomizovane i multicentrične retrospektivne studije potvrđuju efikasnost i sigurnost u lečenju simptomatskih nefunkcionalnih nodusa. **Radiofrekvetna ablacija** predstavlja sve prisutniju metodu u lečenju papilarnog mikrokarcinoma. Može se koristiti za zbrinjavanje medularnog karcinoma ukoliko je hirurški pristup kontraindikovan. Takođe je jedan od modaliteta lečenja rekurentnih cističnih lezija nakon tretmana etanolom ili simptomatskih nodusa sa velikom cističnom komponentom**. Mikrotalasna ablacija** je metoda u razvoju kod koje je zapaženo signifikantno povlačenje simptoma i korekcija estetskih problema bez narušavanja funkcije štitaste žlezde, međutim povezuje se sa većim rizikom od komplikacija**. Fokusirani ultra-zvuk visokog intenziteta** se izvodi kompjuterskim navođenjem i planiranjem, što dovodi do poštede okolnog zdravog tkiva štitaste žlezde. Zbog nedovoljne efikasnosti preporučuje se samo u slučaju kada nema drugih terapijskih opcija. **Perkutano apli- kovanje etanola** prema novim smernicama, predstvalja metodu izbora za relapsne i simptomatske benigne cistične lezije i za čvorove sa tečnom komponentom. **Zaključak**. Do skoro je lečenje čvorova štitaste žlezde podrazumevalo hirurišku intervenciju dok danas postoje superiornije minimalno invazivne tehnike.

**Ključne reči:** tiroidni nodusi; minimalno invazivne hirurške procedure; tehnike ablacije; laserska terapija; etanol; fokusirani ultrazvuk visokog intenziteta; mikrotalasi; radiofrekventna ablacija

✉ Corresponding author: Nikolina Vuković, E-mail: 910060d23@mf.uns.ac.rs, radoslav.pejin@mf.uns.ac.rs

***Abbreviations***

| | |
|---|---|
| T4 | – thyroxine |
| TSH | – Thyroid Stimulating Hormone |
| T3 | – triiodothyronine |
| TBG | – thyroid-binding globulin |
| AITD | – autoimmune thyroid diseases |
| US | – ultrasonography |
| MRI | – magnetic resonance imaging |
| CT | – computerized tomography |
| FDG | – fluorodeoxyglucose |
| FNA | – fine needle aspiration |
| LTA | – laser thermal ablation |
| RFA | – radiofrequency ablation |
| HIFU | – high-intensity focused ultrasound |
| MWA | – microwave ablation |
| PEI | – percutaneous ethanol injection |
| TI-RADS | – Thyroid Imaging Reporting and Data Systems |

## Introduction

The thyroid gland is a bilobed endocrine organ connected by a thin isthmus and enclosed by two capsules [1,2]. Posterior to the gland lie the recurrent laryngeal nerves and the parathyroid glands. Iatrogenic injury to the recurrent laryngeal nerve may result in voice disturbances, whereas damage to the parathyroid glands can lead to hypocalcemia and tetanic symptoms. Despite its superficial anatomical position, the thyroid gland is physiologically non-palpable owing to its soft consistency. Thyroid enlargement typically progresses posteriorly or retrosternally due to resistance from the infrahyoid muscles, whereas large goiters may extend anteriorly and become visibly apparent. Structurally and functionally, the gland consists of numerous secretory follicles responsible for the synthesis of thyroxine (T4) and triiodothyronine (T3).

Thyroid hormone production is regulated by a feedback mechanism involving T3, T4, and thyroid stimulating hormone (TSH). Thyroxine-binding globulin (TBG) is the primary transport protein for T4 in circulation, and its concentration may vary under different physiological and pathological conditions, such as pregnancy. Thyroid hormones are essential for normal tissue development and metabolic regulation. They stimulate cell division and differentiation, regulate lipid, carbohydrate, and electrolyte metabolism, influence enzyme and protein synthesis and activity, promote the expression of catecholamine receptors, support mammary gland development and function , and inhibit the secretion of TSH and prolactin from the anterior pituitary gland [3,4]. Adequate hormone synthesis required a minimum iodine intake of approximately 1 mg per week. Disorders of the thyroid gland arise from dysfunction of the hypothalamic-pituitary-thyroid axis and manifest clinically as hypothyroidism or hyperthyroidism. These conditions are classified as primary, secondary, or tertiary depending on whether the underlying defect originates in the thyroid gland, pituitary gland, or hypothalamus, respectively [5].

## Thyroid nodule

On ultrasonographic examination, a thyroid nodule is defined as a focal lesion that is clearly distinguishable from the surrounding tissue [6]. Nodular thyroid disease can be categorized into three main entities: solitary thyroid nodules, multinodular goiter, and thyroid nodules associated with autoimmune thyroid disease (AITD). Autoimmune thyroid disorders are primarily represented by Graves–Basedow disease and Hashimoto's thyroiditis, which differ substantially in their pathophysiology [7]. Thyroid nodules occur more frequently in older individuals, females, patients with iron deficiency, and those with a history of thyroid irradiation [8].

From a clinico-pathological perspective, thyroid nodules are classified into three principal groups: pseudonodules (hyperplastic and inflammatory lesions, including acute and subacute thyroiditis and Hashimoto's thyroiditis), benign neoplasms (afunctional cold nodules – solid and cystic – and functional hot nodules, such as adenomas), and malignant neoplasms. Malignant lesions include primary thyroid cancers – papillary, follicular, anaplastic, and medullary carcinomas – as well as lymphomas and metastatic tumors [9]. Functionally, nodules are classified as "hot" or "cold" based on radionuclide uptake. Hot nodules demonstrate increased isotope uptake and autonomous hormone production, whereas cold nodules, which account for more than 80% of all thyroid nodules, exhibit reduced uptake [10].

Thyroid nodules can be detected through patient self-examination, clinical palpations, or incidentally during imaging studies such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) of the neck. Ultrasound represents the primary diagnostic modality for nodule detection and characterization, allowing detailed assessment of size, margins, contours, echogenicity, homogeneity, presence of a peripheral halo, calcifications, extracapsular extension, echo signal amplification, edge artifacts, and reverberation phenomena. Additionally, ultrasound guidance is essential for fine needle aspiration (FNA) and for percutaneous treatment of selected lesions [6].

Thyroid scintigraphy is performed using various radiopharmaceuticals, most commonly radioactive iodine isotopes or technetium-99m pertechnetate. Based on radionuclide uptake relative to normal thyroid tissue, nodules are classified as "hot", "warm", or "cold." Hot nodules exhibit increased uptake, warm

nodules show uptake comparable to surrounding tissue, and cold nodules demonstrate reduced uptake.

Scintigraphy provides valuable functional information that assists in diagnostic stratification and therapeutic decision-making. Hot nodules are generally considered benign, and management depends on nodule size and the presence of clinical or biochemical thyrotoxicosis. In contrast, hypofunctioning cystic nodules are typically evaluated using FNA cytology, which may also have a therapeutic effect. For solid or partially cystic cold nodules, treatment decisions are guided primarily by cytological findings.

Fine-needle aspiration cytology is a cornerstone of thyroid nodule evaluation and is recommended for nodules larger than 1 cm. Interpretation should be performed exclusively by experienced cytopathologists. Surgical management is determined based on cytological results, whereas advanced imaging modalities are reserved for selected cases. Although more than 85% of thyroid nodules are cold, only approximately 20% of these lesions are malignant. The risk of malignancy in hypofunctioning nodules is higher in individuals younger than 30 or older than 60 years, in males, and in populations from iodine-deficient regions. Hot nodules account for approximately 5% of all thyroid nodules, with prevalence varying according to regional iodine intake, and carry a very low risk of malignancy. The remaining 15% of nodules are isoactive and demonstrate minimal malignant potential [11].

**Fine-needle aspiration biopsy (FNAB)** represents the cornerstone of preoperative assessment for thyroid nodules due to its reliability, simplicity, and favorable safety profile. Cytological evaluation obtained through FNAB forms the basis of Thyroid Imaging Reporting and Data Systems (TI-RADS) classification and plays a pivotal role in determining optimal management strategies, ranging from surgical intervention to nonoperative surveillance [12]. Each thyroid nodule should be independently assessed to determine the indication for FNAB. Cytological samples are processed and categorized according to the Bethesda System into six diagnostic groups: nondiagnostic (5-10% malignancy risk), benign (0-3% risk), atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) (10-30% risk), follicular neoplasm (FN) or suspicious for follicular neoplasm (SFN) (25-40% risk), suspicious for malignancy (50-75% risk), and malignant (97-99% risk) [6].

## Minimally invasive approaches for the management of benign thyroid nodules

**Laser thermal ablation (LTA)** is a minimally invasive technique that utilizes laser-generated heat to induce coagulation necrosis within targeted thyroid tissue. This approach results in significant nodule volume reduction, symptom relief, and improved cosmetic outcomes while minimizing patient discomfort. Contemporary guidelines, provide strong evidence for the safety, efficacy, and high tolerability of LTA as an alternative to surgery. LTA has emerged as a low-risk and effective treatment for clinically manifest cold nodules, achieving sustained volume reduction and symptomatic improvement. The procedure is generally well tolerated, with most adverse events being mild and transient, including cervical swelling, localized discomfort, minor bleeding, hematoma formation, or low-grade fever. Rare but more serious complications include thyroid dysfunction, autoimmune reactions, laryngeal impairment, vocal cord paralysis, and damage to adjacent cervical structures. Although LTA is not considered first-line therapy for hot nodules or multinodular goiter, conditions for which radioactive iodine therapy or surgery remain superior, it may be considered in selected cases, such as solitary modest-sized hot nodules in patients unfit for standard treatments or as adjunctive therapy in recurrent or residual papillary thyroid carcinoma [6,13].

**Radiofrequency ablation (RFA)** has gained widespread acceptance as a minimally invasive modality for treating benign thyroid nodules, offering favorable cosmetic results and a lower incidence of postprocedural hypothyroidism compared with thyroidectomy [14]. RFA operates by generating an alternating electric field that causes ionic oscillation, resulting in localized thermal injury and tissue necrosis. It is primarily indicated for nodules producing compressive symptoms or cosmetic concerns and may be employed in patients with recurrent thyroid carcinoma who are unsuitable for surgery. Due to limited long-term oncological data, RFA is not recommended as primary therapy for thyroid malignancies. The procedure is performed under continuous ultrasound guidance using either the moving-shot technique – particularly effective for the treatment of oval-shaped nodules – or the trans-isthmic approach, which enhances needle stability and reduces the risk of displacement during movement, phonation, or coughing. Real-time ultrasound visualization of critical neck structures, including the recurrent laryngeal nerve, further improves procedural safety [13]. Beyond benign disease, RFA has demonstrated utility in selected cases of papillary thyroid microcarcinoma and in medullary thyroid carcinoma when surgery is contraindicated [15,16]. Additionally, it is effective for treating recurrent cystic nodules after ethanol ablation and nodules with persistent solid components that continue to cause symptoms [17].

**Microwave ablation (MWA)** is a relatively novel minimally invasive technique, although clinical experience and available evidence remain limited. Preliminary data suggest a potentially higher incidence of unexpected adverse events compared with LTA and RFA, likely due to less precise energy control and the larger caliber of applications. Currently, robust studies evaluating the efficacy and safety of MWA in autonomously functioning thyroid nodules are lacking, underscoring the need for further investigation [17].

**High intensity focused ultrasound (HIFU)** is a noninvasive technique that induces coagulative necrosis through the focused delivery of ultrasound energy while reserving skin integrity. Due to the limited volume treated per application, multiple sessions are often required to achieve adequate ablation, resulting in prolonged procedural times. Advanced computer-assisted planning allows precise delineation of treatment boundaries, minimizing damage to the surrounding tissues [13]. Compared with RFA and LTA, HIFU demonstrates lower therapeutic efficacy, higher costs, and a more limited evidence base. Consequently, its use is generally restricted to carefully selected patients who are not candidates for other treatment modalities or with structured clinical research protocols [17]. Although HIFU is associated with a relatively low complication rate, the extent of nodule volume reduction remains modest [13].

**Percutaneous ethanol injection (PEI)** is a targeted ablative therapy involving direct injection of ethanol into thyroid nodules, leading to coagulative necrosis, endothelial injury, and vascular occlusion. This results in ischemia and definitive ablation of the lesion. PEI is considered the first-line treatment for recurrent or clinically significant benign cystic nodules and for nodules with a predominant cystic component, owing to its favorable safety profile, good tolerability, cost-effectiveness and low recurrence rate. It may also be considered when other therapeutic options are contraindicated or unavailable. However, repeated treatment sessions can cause perinodular fibrosis due to ethanol leakage, potentially complicating future surgical interventions. Therefore, PEI is generally reserved for solid benign nodules only when more advanced ablative techniques are unsuitable [17].

## Conclusion

Historically, the management of thyroid nodules relied predominantly on surgical intervention. Advances in minimally invasive technologies have introduced effective alternatives with reduced morbidity and improved patient acceptance. Percutaneous ethanol injection is primarily indicated for cystic or predominantly cystic thyroid nodules, whereas laser thermal ablation and radiofrequency ablation are effective options for benign nodules irrespective of functional status, particularly in patients who are poor surgical candidates, ineligible for radioactive iodine therapy, or who decline these treatments. In cases of recurrent papillary thyroid carcinoma, laser thermal ablation, percutaneous ethanol injection, and radiofrequency ablation may represent feasible nonsurgical options for patients unsuitable for repeat surgery. Although microwave ablation and high-intensity focused ultrasound currently lack sufficient high-quality evidence to support widespread use, early results appear promising. Further well-designed studies are necessary to establish the long-term efficacy and optimal role of high-intensity focused ultrasound, despite its lower complication rate, is associated with relatively limited nodule volume reduction.

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Rad je primljen 5. XI 2025.
Recenziran 16. XII 2025.
Prihvaćen za štampu 5. I 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:265-269.

# EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS – A COMPREHENSIVE NARRATIVE REVIEW

# *EOZINOFILNA GRANULOMATOZA SA POLIANGIITISOM – SVEOBUHVATNI PREGLEDNI ČLANAK*

**Slobodan ŠAJINOVIĆ[1,2], Vladimir ĐUROVIĆ[1,2], Sonja GOLUBOVIĆ[1,2], Aleksandra BUKVIĆ ŠAJINOVIĆ[1], Dejan ĆELIĆ[1,2] and Milica POPOVIĆ[1,2]**

ORCID NUMBER
Slobodan Šajinović – 0009-0004-0519-3400
Sonja Golubović – 0000-0003-3716-698X
Aleksandra Bukvić Šajinović – 0009-0003-5578-4412
Milica Popović – 0000-0002-0124-9444

University of Novi Sad, Faculty of Medicine Novi Sad[1]
University Clinical Center of Vojvodina, Novi Sad
Clinic for Nephrology and Clinical Immunology[2]

Review article
*Pregledni članak*
UDK 616-002.7-097-07/-08:615.357
https://doi.org/10.2298/MPNS2512270S

**Abstract**

**Introduction.** Eosinophilic granulomatosis with polyangiitis is a rare, systemic, immune-mediated vasculitis of small- to medium-sized blood vessels, characterised by eosinophil-rich inflammatory response, necrotising vasculitis, and granulomatous tissue reactions. **Pathogenesis.** The disease arises from a complex interplay of T helper 2- and T helper 1 cells mediated immunity, eosinophil activation, B-cell-autoantibody responses, and epithelial-derived alarmins. Anti-neutrophil cytoplasmic antibodies positive (predominantly myeloperoxidase) patients exhibit a vasculitic phenotype, whereas anti-neutrophil cytoplasmic antibodies-negative patients show eosinophil-driven organ involvement. Key laboratory features include marked peripheral eosinophilia, elevated inflammatory markers, increased immunoglobulin E levels, and raised immunoglobulin G4 level. **Clinical Presentation.** The disease evolves through overlapping prodromal, eosinophilic, and vasculitic phases, producing variable organ involvement and a relapsing-remitting course. Heterogeneous presentation may obscure diagnosis and affect prognosis. **Diagnosis and Differential Diagnosis.** Diagnosis integrates clinical features, laboratory findings, and histopathologicy analysis. Differential diagnoses include other anti-neutrophil cytoplasmic antibody-associated vasculitides, hypereosinophilic syndromes, eosinophilic lung disorders, drug-induced reactions, parasitic infections, and immunoglobulin G4-related disease. **Prognosis.** Despite limited evidence, overall survival is generally favourable. **Therapy.** Management is guided by severity and prognostic factors. Glucocorticoids remain foundational, while biologics targeting interleukin-5, interleukin-4/interleukin-13, anti-immunoglobulin E – as well as emerging approaches including B-cell depletion, alarmin inhibition, C5a receptor antagonism, and cellular therapies provide steroid-sparing options and improved disease control. **Conclusion.** Despite favorable survival, morbidity persists due to disease relapses, organ-specific complications, and long-term immunosuppression. Advances in immunogenetics, molecular profiling, and targeted therapies support a precision–medicine approach, multidisciplinary care and individualised management to optimise patient outcomes in eosinophilic granulomatosis with polyangiitis.

**Key words:** Granulomatosis with Polyangiitis; Eosinophilia; Vasculitis; Purpura; Asthma

**Sažetak**

**Uvod.** Eozinofilna granulomatoza sa poliangiitisom je retka sistemska imunoposredovana bolest koja zahvata male i srednje krvne sudove. Karakteriše se eozinofilnom infiltracijom tkiva praćenom nekrotizirajućim vaskulitisom i stvaranjem granuloma. **Patogeneza.** Bolest nastaje usled složene interakcije celularnog i humoralnog imuniteta, aktivacije eozinofila i alarmina epitelijalnog porekla. Pacijenti koji imaju pozitivna antineutrofilna citoplazmatska antitela pokazuju češće vaskulitisni oblik bolesti, dok pacijenti sa negativnim antitelima češće razvijaju eozinofilima posredovano oštećenje organa. **Klinička slika.** Bolest se razvija kroz tri faze (prodromalnu, eozinofilnu i vaskulitisnu) koje se često međusobno preklapaju. Zahvatanje organa je nespecifično, ali su najčešće zahvaćeni respiratorni i periferni nervni sistem i koža. Bolest ima relapsirajući karakter. Heterogena prezentacija može otežati dijagnozu i uticati na prognozu. **Dijagnoza i diferencijalna dijagnoza.** Dijagnoza se zasniva na kliničkim manifestacijama, laboratorijskim nalazima i histopatologiji. Diferencijalna dijagnoza obuhvata druge vaskulitise povezane sa pozitivnim antineutrofilnim citoplazmatskim antitelima, hipereozinofilne sindrome, eozinofilne plućne bolesti, reakcije na lekove, parazitske infekcije i imunoglobulin G4-povezanu bolest. **Prognoza** za ove pacijente je dobra. **Terapija.** Lečenje je uslovljeno težinom kliničke slike i prognostičkim faktorima. Kortikosterodi su i dalje osnova terapije, dok biološki lekovi usmereni protiv interleukina 5, interelukina 4 i 13, anti-imunoglobulina E i nove strategije poput B-limfocitne deplecije, blokade alarmina, antagonizma C5a receptora i ćelijskih terapija pružaju mogućnost smanjenja upotrebe kortikosteroida i bolje kontrole bolesti. **Zaključak.** Uprkos povoljnoj stopi preživljavanja, morbiditet i dalje postoji zbog relapsirajućeg karaktera bolesti, sistemskih komplikacija i posledice dugotrajne imunosupresivne terapije. Napredak u imunogenetici, molekularnom profilisanju i ciljanim terapijama podržava pristup terapije bez kortikosteroida, naglašavajući značaj multidisciplinarne nege i individualizovanog pristupa za optimizaciju ishoda bolesti.

**Ključne reči**: granulomatoza sa poliangitisom; eozinofilija; vaskulitis; purpura; astma

✉ Corresponding author: Slobodan Šajinović, E-mail: slobodan.sajinovic@mf.uns.ac.rs

***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
IL – interleukin
IgG4 – immunoglobulin G4
Th1 – T helper type 1 cells, Treg – regulatory T cells
IFN-γ – interferon gamma
TNF-α – tumour necrosis factor alpha
WBC – white blood cells
Eos – eosinophils
CRP – C-reactive protein
ESR – erythrocyte sedimentation rate
GPA – granulomatosis with polyangiitis
MPA – microscopic polyangiitis
AZA – azathioprine
MTX – methotrexate
RTX – rituximab
CYC – cyclophosphamide
ENT – ear, nose, throat
TMP/SMX – trimethoprim-sulfamethoxazole
FFS – Five-Factor Score
GC – glucocorticoid
JAK – Janus kinase
Siglec-8 – sialic acid-binding immunoglobulin-like lectin

## Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare, immune-mediated disorder characterised by necrotising vasculitis of small- to medium-sized blood vessels accompanied by prominent eosinophilic infiltration and granulomatous tissue inflammation [1–5]. The condition was first described in the early 1950s by Churg and Strauss, who identified a group of patients presenting with asthma, marked eosinophilia, and multisystem involvement caused by necrotising, eosinophil-rich vasculitis and granulomatous inflammation. Based on these shared clinicopathological features, they proposed the entity initially termed *allergic granulomatosis* [6]. A few years later, comparative studies by Churg and Godman demonstrated that this syndrome, together with granulomatosis with polyangiitis and microscopic polyangiitis, constituted a distinct group of small-vessel *pauci-immune* vasculitides, separable from classic polyarteritis nodosa. This work laid the foundation for the modern classification of EGPA [7].

This narrative review provides a comprehensive overview of EGPA, focusing on its clinical manifestations, underlying immunopathological mechanisms, and current as well as emerging therapeutic strategies, while highlighting recent advances in diagnosis, risk stratification, and targeted therapy.

## Incidence and Prevalence

The estimated annual incidence of EGPA ranges from 0.5 to 4.2 cases per million inhabitants, although reported figures vary considerably, largely due to differences in applied classification criteria [5,8,9]. The disease most commonly affects individuals between 40 and 60 years of age [10], with no significant difference between males and females [1,9]. Reported prevalence rates vary widely worldwide, ranging from approximately 2 cases per million in Germany to as high as 30 per million in Norway, with no consistent associations identified with temporal trends, geographic region, or specific diagnostic criteria [2].

## Pathogenesis

The pathogenesis of EGPA is influenced by both genetic predisposition [2,11] and environmental exposures, including organic solvents, silica, and farming-related factors [12,13]. Accumulating evidence indicates that EGPA is a polygenic and heterogeneous disease composed of distinct antineutrophil cytoplasmic antibodies (ANCA)-defined endotypes, each characterised by unique genetic backgrounds, immune pathways, and clinical features.

Data from the European Vasculitis Genetics Consortium demonstrated that EGPA comprises two genetically distinct entities. The myeloperoxidase (MPO)-ANCA-positive form is associated with HLA-DQ alleles and exhibits a phenotype that overlaps with classical autoimmune vasculitides [14]. In contrast, ANCA-negative EGPA is associated with non-HLA genetic variants involved in epithelial barrier integrity and eosinophil regulation, supporting fundamentally divergent pathogenic mechanisms between these two subsets [14].

At the immunological level, EGPA pathogenesis reflects the interaction between epithelial-derived alarmins, T helper 2 inflammation, eosinophil-mediated tissue injury, and B-cell/autoantibody production, with MPO-ANCA characterizing the vasculitic phenotype [15,16]. Environmental factors appear to further modulate disease susceptibility and clinical expression of ANCA-associated vasculitis (AAV), with the strongest evidence supporting roles for silica exposure, microbial triggers such as *Staphylococcus aureus*, farming, and certain medications, including penicillins, cephalosporins, phenytoin, and allopurinol [12]. Other proposed contributors – such as air pollution, seasonal variation, and viral infections - remain inconsistently supported across studies [13].

### Immunological Pathways

EGPA is driven by dysregulation of T-cell responses, characterized by dominant T helper 2 (Th2) cytokine activity, including interleukin (IL)-3, IL-4, IL-5, IL-9, IL-10, IL-13, and IL-25, together with an antigen-driven T-cell repertoire. Additional immune imbalance arises from dysregulation of Th17/T regulatory (Treg) axis, which further amplifies inflammation through neutrophil recruitment. Increased interferon-γ (IFN-γ) production and activation of cytotoxic $CD8^+$ T cells reflect additional Th1-mediated vascular damage [17].

In ANCA-positive EGPA, B cells and neutrophils participate in a self-perpetuating inflammatory loop. Proinflammatory cytokines prime neutrophils to expose ANCA antigens, facilitating ANCA binding and subsequent neutrophil activation. This results in the release of reactive oxygen species (ROS), enzymes, and the formation of neutrophil extracellular traps (NETs), which in turn stimulate B cells to produce additional ANCA, perpetuating vascular injury [15–17].

Eosinophils, activated predominantly by IL-5, IL-4, and IL-13, migrate from the bone marrow to peripheral tissues, where they persist and contribute to EGPA through cytotoxic, inflammatory, and non-immunological mechanisms. Th2-derived cytokines establish a positive feedback loop that drives eosinophila rise [5,18]. Epithelial-derived alarmins – including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) – play a critical upstream role by promoting eosinophil differentiation and survival [5,17]. Collectively, these advances identify key pathways, including the IL-5-eosinophil axis, epithelial alarmins, and B-cell/IgG4 networks, providing biomarkers of disease activity and supporting the development of targeted biologic therapies [15,16].

### Heterogeneous Clinical Presentation

The clinical presentation of EGPA is highly heterogeneous and frequently involves multiple organ systems. If left untreated, the disease may progress to severe or irreversible multiorgan damage [3–5]. EGPA typically follows a relapsing-remitting course, with more than one-third of patients experiencing relapse within five years of achieving initial remission [2].

Classically, EGPA evolves through prodromal, eosinophilic, and vasculitic phases, although these often coexist, contributing to diagnostic delay [18,19]. The **prodromal phase** is dominated by asthma, allergic rhinitis, and chronic sinusitis, and may persist for several years. The **eosinophilic phase** characterised by marked peripheral eosinophilia and eosinophilic infiltration of tissues, most commonly affecting the lungs, gastrointestinal tract, and heart [1, 5,20]. The **vasculitic phase** involves systemic necrotising small- to medium-sized vessels, resulting in organ-specific manifestations and constitutional symptoms, with ANCA positivity most frequently associated with this stage [1,2,5,15,20].

Approximately one-third of patients with EGPA are ANCA-positive, most commonly exhibiting MPO specificity [1,8]. Clinical manifestations vary according to ANCA status. ANCA-positive patients more frequently exhibit vasculitic features such as glomerulonephritis, peripheral neuropathy, and purpura [21,22]. In contrast, ANCA-negative patients tend to display predominantly eosinophilic manifestations, including cardiac involvement and gastroenteritis. Nonetheless, most patients demonstrate overlapping vasculitic and eosinophilic phenotypes [8,23,24].

Once diagnosed, EGPA may follow either mild, self-limiting course or progress to severe, multi-organ involvement associated with substantial morbidity and mortality [25]. Constitutional symptoms such as fever, weight loss, and fatigue are common and reflect systemic inflammation [4,8,18,26], often accompanied by cutaneous manifestations [24,27]. The severity and prognostic significance of organ involvement vary considerably, and some manifestations may remain underrecognised due to the absence of standardised diagnostic criteria [1,3,4]. **Table 1** summarizes organ involvement frequency, clinical manifestations, and ANCA positivity for each organ system in EGPA.

### Diagnosis Criteria and Differential Diagnosis

The diagnosis of EGPA relies on an integrated assessment of characteristic clinical features, laboratory findings, and histopathological confirmation from tissue biopsy [5,8,20]. Key laboratory features include marked peripheral eosinophilia, typically exceeding $1.5 \times 10^9$/L or 10% of circulating leukocytes (often reaching 5,000–9,000/μL), elevated non-specific inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), increased serum IgE, and elevated IgG4 levels [5,10].

Although the complement system may contribute to disease pathogenesis in specific contexts [28], complement levels are not routinely considered clinically informative in EGPA [5]. In clinical practice and research settings, including clinical trials, diagnosis and classification commonly rely on the American College of Rheumatology (ACR) criteria and the European Alliance of Associations for Rheumatology (EULAR) recommendations [2,5,29] **(Table 2).**

The differential diagnosis of EGPA is broad and includes other small-vessel vasculitides as well as nu-

**Table 1.** Frequency and characteristics of organ involvement in EGPA

| Organ/System | Frequency | Typical Manifestations | ANCA Association | References |
|---|---|---|---|---|
| Constitutional | Very common | Fever, fatigue, weight loss | Non-specific | [2,4,5,8,27] |
| Skin | Common | Palpable purpura, subcutaneous nodules, pruritus, ulcers, urticaria, splinter hemorrhages | Vasculitic features in ANCA-positive | [2,8,25,28] |
| Respiratory | Very common | Asthma (often severe, steroid-dependent), chronic rhinosinusitis, nasal polyps, recurrent pneumonia/bronchitis, eosinophilic pulmonary infiltrates, chronic cough, dyspnea, bronchiolitis | Both eosinophilic and vasculitic phenotypes | [5,8,27,31] |
| Gastrointestinal | Moderate | Abdominal pain, nausea, vomiting, diarrhea, systemic inflammation | ANCA-negative more likely eosinophilic involvement | [4,49] |
| Cardiac | Variable | Myocarditis, pericarditis, arrhythmias, heart failure, cardiac thrombi | Often eosinophilic and vasculitic phase | [3,4,5] |
| Neurologic | Common | Mononeuritis multiplex, distal polyneuropathy, paresthesia, cranial nerve deficits, CNS involvement (stroke, TIA, seizures) | ANCA-positive more vasculitic | [2,4,26] |
| Renal | Variable | Glomerulonephritis, hematuria, proteinuria, AKI/CKD, renal infarcts, eosinophilic infiltration | Mostly ANCA-positive | [47,50] |
| Musculoskeletal | Common | Arthralgia, myalgia, occasionally inflammatory arthritis | Non-specific | [28,36,39] |
| Hematologic | Very common | Peripheral eosinophilia, leukocytosis, thrombocytosis, mild anemia; rare hypercoagulability | Eosinophil-mediated | [11,20] |
| Ophthalmologic | Rare | Conjunctivitis, episcleritis, uveitis, orbital pseudotumor, optic neuritis | Small-vessel vasculitis or eosinophilic | [9,41] |

CNS – central nervous system; TIA – transient ischemic attack; AKI – acute kidney injury; CKD – chronic kidney disease

merous eosinophilic disorders. Distinction from granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) is usually achievable based on clinical and histological features, although overlapping eosinophilia or PR3-ANCA positivity may complicate differentiation in rare cases [23]. Secondary causes of eosinophilia must be systematically excluded. Drug-indicted reactions and helminthic infections are key considerations, with serological testing for *Toxocara canis* and *Strongyloides stercoralis* particularly recommended [16]. EGPA also shares features with eosinophilic lung disorders, making differential diagnosis essential once peripheral eosinophilia is detected. Chronic eosinophilic pneumonia, frequently associated with asthma, is typically limited to pulmonary involvement and lacks the systemic vasculitic manifestations characteristic of EGPA [30]. Hypereosinophilic syndrome (HES) represents another important differential diagnosis, characterised by sustained eosinophilia and eosinophil-mediated organ damage. However, but asthma is neither required nor common in HES, and ANCA

**Table 2.** College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for EGPA

| EGPA patients are classified after establishing the diagnosis of small- or medium-vessel vasculitis, provided that alternative conditions that may mimic vasculitis have been thoroughly excluded before applying the criteria. | |
|---|---|
| Clinical criteria | |
| Feature | Score |
| Obstructive airway disease | 3 |
| Nasal polyps | 3 |
| Mononeuritis multiplex | 1 |
| Laboratory and biopsy criteria | |
| Feature | Score |
| Blood eosinophil count ≥ $1 \times 10^9$/L | 5 |
| Extravascular eosinophilic-predominant inflammation on biopsy | 2 |
| Positive test for cytoplasmic ANCA [c-ANCA] or anti-PR3 antibodies | –3 |
| Haematuria | –1 |
| Sum the scores for all 7 items if present. EGPA classification requires a total score of ≥ 6 | |

positivity is typically absent [31]. In addition, non-myeloid malignancies can cause secondary hypereosinophilia and must be excluded [32,33]. Our previous work on HIV-associated lymphomas [34] demonstrated that delayed recognition of underlying pathology and advanced immune dysfunction significantly worsen outcomes, underscoring the importance of timely and accurate etiological diagnosis in patients presenting with eosinophilia.

Although elevated IgG4 levels are observed in a subset of EGPA patients, IgG4-related disease lacks the defining vasculitic features of EGPA [35]. When all secondary causes are excluded, idiopathic HES or other rare HES variants should be considered [32].

**Therapy**

The management of EGPA is primarily guided by disease severity and prognostic indicators, most commonly assessed using the Five-Factor Score (FFS) [5,17,36]. Patients presenting with non-severe disease (FFS = 0) are generally treated with glucocorticoid (GC) monotherapy. In the majority of cases, remission can be achieved; however, relapse is common, particularly during dose tapering [5,36].

In patients with relapsing or refractory non-severe disease, mepolizumab (300 mg administered subcutaneously once monthly) is recommended due to its proven efficacy in reducing relapse rates and its substantial steroid-sparing effect. Additional immunosuppressive agents, including azathioprine (AZA), methotrexate (MTX), mycophenolate, or rituximab (RTX), may be considered on an individual bases according to patient characteristics [2,5,8,36].

Patients with severe or organ- and life-threatening manifestations (FFS ≥1) require induction therapy with high-dose GC in combination with intravenous cyclophosphamide (CYC), preferably administered in pulsed regimens to limit cumulative toxicity [8,20,37]. RTX represents an effective alternative in situations where CYC is contraindicated, such as in patients requiring fertility preservation [36].

Maintenance therapy following induction typically avoids CYC use because of its long-term toxicity profile. Commonly employed agents include MTX, AZA, RTX, or mepolizumab. In relapsing patients without poor prognostic factors, mepolizumab is generally preferred [2,5,36].

The oral C5a receptor inhibitor avacopan has demonstrated efficacy in the management of severe GPA and MPA, enabling substantial reductions on glucocorticoid exposure while maintaining disease remission. Accordingly, avacopan has been incorporated into the 2024 KDIGO recommendations [38]. Tumour necrosis factor-α (TNF-α) inhibitors, such as etanercept, which are widely used in rheumatoid arthritis [39], are not recommended in EGPA due to the lack of demonstrated clinical benefit and concerns regarding safety in this patient population [40].

Biologic therapies now occupy a central role in the management of relapsing or refractory EGPA [41]. Mepolizumab has shown efficacy irrespective of ANCA status, whereas other IL-5-targeting agents (reslizumab, benralizumab) and anti-IgE therapy (omalizumab) are supported by more limited evidence and are generally reserved for selected cases [36,41]. Dupilumab may be beneficial in patients with prominent asthma or ENT involvement, although caution is warranted due to its potential to exacerbate eosinophilia [5,36]. The combination of dupilumab and mepolizumab may represent a safe and effective therapeutic strategy in selected patients with EGPA [42].

At present, no EGPA-specific protocol for GC tapering exists, and regimens used in GPA/MPA are frequently applied as guidance. Patients with persistent asthma or ENT involvement may require slower and more prolonged tapering, underscoring the importance of multidisciplinary management [36,43]. Follow-up should be guided by structured clinical assessment rather than reliance on laboratory findings alone. Although ANCA titers, eosinophil counts or CD19+ B-cell levels are routinely monitored, disease activity is best evaluated using validated clinical assessment instruments [17]. Among these, the Birmingham Vasculitis Activity Score and the Vasculitis Damage Index are widely recommended to distinguish active inflammation from irreversible organ damage [2,5]. Recent advances in the management of ANCA-associated vasculitis and EGPA have increasingly focused on minimizing GC exposure while maintaining durable disease control [38]. Infection prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) is recommended for patients receiving RTX, CYC, or prolonged high-dose GC therapy to prevent *Pneumocystis jirovecii* and other opportunistic infections [44,45]. A systematic review suggests that intermittent TMP/SMX regimens are better tolerated than daily dosing while providing comparable prophylactic efficacy [45]. Alternative options include dapsone, atovaquone, or aerosolized pentamidine.

Vaccination strategies should adhere to current EULAR recommendations for patients with autoimmune diseases [46]. In addition, monitoring serum immunoglobulin levels prior to RTX therapy is essential to detect secondary hypogammaglobulinemia, which may develop in a substantial proportion of patients receiving long-term RTX or CYC [43].

### Future Therapeutic Approaches

Systemic glucocorticoids continue to form the cornerstone of EGPA therapy. However, the introduction of biologics targeting IL-5 and IL-4/IL-13 pathways has markedly improved disease management. Ongoing research is increasingly focused on upstream targets within the inflammatory cascade, including epithelial-derived alarmin inhibition (tezepelumab), B-cell depletion approaches, and novel agents such as Janus kinase (JAK) and Siglec-8 inhibitors [15,38]. Furthermore, CD19-targeted chimeric antigen receptor (CAR) T–cell therapy has demonstrated promising results in refractory ANCA-associated vasculitis, leading to profound B–cell depletion and reduction in autoantibody levels [47,48]. Although clinical data in EGPA are not yet available, this approach may ultimately offer a therapeutic option for patients with severe, treatment-resistant disease.

### Prognosis and Outcomes

Despite the rarity of EGPA and the limited evidence, overall survival is generally favourable. White and Dubey reported – to 7-year survival rates of approximately 90-96%, although patients aged 65 years or older exhibited an increased risk of mortality [5]. Nonetheless, mortality rates remain heterogeneous across cohorts. Doline reported that EGPA-related mortality may exceed that of the general population, particularly among patients with relapsing or refractory disease or those requiring prolonged GC therapy [9]. An American cohort study reported an overall mortality of 4%, lower than historical estimates of 7–14%, likely reflecting improvements in early diagnosis and therapeutic strategies [26]. However, EGPA continues to impose a substantial chronic disease burden. Frequent hospital admissions, long-term corticosteroid dependence, and extensive healthcare utilisation negatively affect long-term outcomes and quality of life. Cardiac, renal, and gastrointestinal involvement remain well-established predictors of adverse prognosis [3,9,49,50].

### Conclusion

Eosinophilic granulomatosis with polyangiitis represents a uniquely complex vasculitic disorder situated at the intersection of allergic inflammation, eosinophil-driven tissue injury, and pauci-immune autoimmunity. Accumulating evidence clearly establishes antineutrophil cytoplasmic antibodies-defined endotypes as biologically and clinically distinct entities. Although survival has improved substantially through earlier recognition, structured disease assessment, and the introduction of targeted biologic therapies, eosinophilic granulomatosis with polyangiitis continues to impose a significant long-term burden driven by relapsing disease, chronic glucocorticoid exposure, and organ-specific complications. Advances in understanding the IL-5–eosinophil axis, epithelial alarmins, B-cell and IgG4 networks, and the immunogenetic landscape have transformed both the conceptual framework and clinical management of this disease.

Emerging therapeutics – Including IL-5, IL-4/Il-13 blockade, alarmin inhibition, B-cell depletion strategies, Janus kinase and Siglec-8 inhibitors, C5a receptor antagonists, and early exploration of CD19-directed cellular therapies – signal a paradigm shift toward precision, steroid-sparing treatment algorithms. Nevertheless, significant unmet needs persist, including optimized glucocorticoid tapering strategies, risk stratification beyond the Five-Factor Score, reliable biomarkers distinguishing active disease from chronic damage, and evidence-based guidance for long-term follow-up.

Continued integration of immunogenetics, molecular profiling, and real-world outcomes is essential to refine prognostication, personalize therapy, and ultimately reduce the chronic morbidity associated with eosinophilic granulomatosis with polyangiitis. As the therapeutic landscape continues to evolve, multidisciplinary care, vigilant monitoring, and a sustained commitment to minimising treatment-related toxicity will remain central to improving quality of life and long-term outcomes for patients living with this rare but increasingly treatable vasculitis.

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Rad je primljen 4. XII 2025.
Recenziran 18. XII 2025.
Prihvaćen za štampu 18. XII 2025.
BIBLID.0025-8105:(2025):LXXVIII:9-12:270-277.

# THE ROLE OF FLEXIBILITY AND JOINT MOBILITY IN INJURY PREVENTION AND THEIR EFFECT ON PHYSICAL PERFORMANCE

# *ULOGA FLEKSIBILNOSTI I POKRETLJIVOSTI ZGLOBOVA U PREVENCIJI POVREDA I NJIHOV UTICAJ NA FIZIČKE PERFORMANSE*

**Enis GARIPI[1,2], Viktor BRUSNJAI[1,3], Tijana ALEKSANDRIĆ[1,2], Larisa SUBIĆ[1,2], Dunja KOVAČEVIĆ[1,2] and Aleksandar KNEŽEVIĆ[1,2]**

ORCID NUMBER
Enis Garipi – 0000-0002-4384-468X
Viktor Brusnjai – 0009-0009-0337-8977
Tijana Aleksandrić – 0009-0006-1049-064X
Larisa Subić – 0009-0001-3047-7681
Dunja Kovačević – 0009-0003-0587-3396
Aleksandar Knežević – 0000-0002-9297-793X

University of Novi Sad, Faculty of Medicine Novi Sad[1]
University Clinical Center of Vojvodina, Novi Sad
Physical Medicine and Rehabilitation Clinic[2]
Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica[3]

Review article
*Pregledni članak*
UDK 616.72-001-084:796.012.88
https://doi.org/10.2298/MPNS2512278G

**Abstract**

**Introduction**. Flexibility and joint mobility are fundamental determinants of efficient and safe movement execution. They play an important role in injury prevention during daily activities, training, and competitive performance, and substantially influence athletic outcomes. Between the ages of 20 and 49, flexibility declines by approximately 10% per decade. Stretching is one of the primary interventions used to restore, maintain, and enhance flexibility. Evidence suggests that regular and structured stretching programs can preserve joint range of motion and improve mobility. Stretching has also been proposed to enhance physical performance, facilitate post-exercise recovery, and reduce injury risk. **Discussion**. Stretching constitutes an essential component of both athletic training and rehabilitation; therefore, identifying the optimal timing, volume, and intensity of stretching within motor learning and re-education programs is of considerable importance. However, despite widespread application, the scientific literature has not yet reached a clear consensus regarding its effects, as evidence remains inconsistent or insufficient for several commonly cited benefits. The aim of this narrative review is to summarize current evidence on the effects of dynamic and static stretching on injury prevention and physical performance. **Conclusion**. It remains difficult to definitively determine whether stretching exerts predominantly beneficial or adverse effects. Given the heterogeneity and often contradictory findings in the existing literature, stretching protocols should be individualized, with careful consideration of the type, volume, and intensity of stretching in relation to the specific goals of rehabilitation or athletic training.

**Key words:** Joints; Range of Motion, Articular; Athletic Injuries; Muscle Stretching Exercises; Risk Factors; Accident Prevention; Athletic Performance

**Sažetak**

**Uvod**. Fleksibilnost i pokretljivost zglobova su ključni za izvođenje pokreta na optimalan i bezbedan način. Veoma su važni za prevenciju povreda u svakodnevnom životu, tokom treninga i tokom takmičarskog nastupa, te imaju značajan uticaj na sportske performanse. Od 20. do 49. godine dolazi do smanjenja fleksibilnosti za ~10% svake decenije. Jedan od načina za restoraciju, održavanje i poboljšanje fleksibilnosti je proces istezanja. Studije takođe pokazuju, da posvećeno i učestalo istezanje može da očuva obim pokreta u zglobovima, kao i da poveća mobilnost. Smatra se da proces istezanja doprinosi poboljšanju fizičkih performansi, utiče na brzinu oporavka nakon fizičkog napora i smanjuje rizik od povreda. **Diskusija**. Istezanje predstavlja važnu komponentu, kako u sportskom treningu pojedinaca, tako i procesu rehabilitacije, te je od velikog značaja određivanje pravovremenosti, obima i intenziteta istezanja u kontekstu motorne edukacije i reedukacije. Uprkos navedenim činjenicama, u naučnoj zajednici još uvek ne postoji konsenzus po pitanju pomenutih efekata, jer za pojedine ne postoji dovoljno dokaza. Cilj ovog rada je da prikaže aktuelne stavove u vezi sa pozitivnim uticajima dinamičkog i statičkog istezanja na prevenciju povreda i njihov uticaj na fizičke performanse. **Zaključak**. Nije jednostavno doneti sud o tome da li istezanje ima prevashodno pozitivne ili negativne efekte. Kada se uzmu u obzir postojeći, često divergentni rezultati istraživanja na ovu temu, nameće se zaključak da je neophodno prilagoditi vrstu, obim i intenzitet istezanja u odnosu na željeni ishod rehabilitacionog programa ili sportskog treninga.

**Ključne reči:** zglobovi; opseg pokreta zgloba; sportske povrede; vežbe istezanja; faktori rizika; prevencija povreda; sportski učinak

## Introduction

Flexibility and range of motion (ROM) generally refer to the total extent of movement available within a joint or a complex of joints, allowing normal and unrestricted function. These characteristics are influenced by individual, intrinsic, and hereditary properties of connective tissue, tend to decline with aging, and, importantly, can be preserved and enhanced through appropriate exercise interventions [1,2].

As early as 1964, Fleischman demonstrated that flexibility represents an independent component of physical fitness and can be improved through static stretching [3]. Subsequent research has shown that ag-

✉ Corresponding author: Enis Garipi, E-mail: enis.garipi@mf.uns.ac.rs

***Abbreviations***

ACSM – American College of Sports Medicine
DS – dynamic stretching
GTO – Golgi tendon organ
ROM – range of motion
SS – static stretching

ing is associated with reductions in muscle function and flexibility, which may ultimately lead to diminished functional capacity and loss of independence in daily activities [4]. Adequate flexibility of the lower extremity musculature has been linked to a reduced risk of lower back injuries, as well as a lower incidence of spondylolysis and spondylolisthesis [5]. Low back pain is currently the leading cause of disability in 160 countries worldwide [6], with lumbar radiculopathy affecting up to 5% of the general population [7]. Moreover, significant positive correlations have been observed between fear-avoidance behaviors and pain intensity in individuals with lumbosacral radiculopathy [8].

Joint mobility, particularly at the hip, is reduced in patients with hip and knee osteoarthritis [9,10], and stretching has been shown to be an effective intervention for increasing hip abduction ROM [11]. In individuals with lower-limb amputation, limitations in residual limb ROM may negative predict successful prosthetic ambulation [12]; consequently, restricted hip or knee extension is incorporated into several predictive models of ambulation potential with high accuracy [13]. Additionally, greater joint ROM has been associated with a reduced risk of muscle rupture [14].

In clinical practice, ROM is typically assessed as the total movement arc around a joint or joint complex; therefore, the terms *flexibility* and *range of motion* are often used interchangeably. Stretching is defined as the application of tensile force along the rotational or translational plane of joint movement and is traditionally incorporated into training and rehabilitation programs. Two primary stretching modalities are commonly distinguished: static and dynamic stretching.

Despite the widespread use of stretching, scientific literature reports not only beneficial but also potentially adverse effects. One major limitation in drawing definitive conclusions lies in the methodological heterogeneity of existing studies, as the effects of stretching cannot be generalized from protocols that employ highly specific stretching modalities, durations, intensities, and frequencies. Research investigating both the acute and chronic effects of stretching has intensified over the past two decades, yet consensus regarding its overall efficacy remains elusive.

## The Physiology of Stretching

Skeletal muscle exhibits the greatest capacity for elongation and accounts for approximately 95% of the total lengthening of the muscle-tendon unit. Tensile forces applied during stretching also affect surrounding soft tissues, including fasciae, ligaments, joint capsules, nerves, blood vessels, and connective tissue. Nevertheless, this review focuses specifically on the biomechanical and neurophysiological mechanisms underlying muscle stretching.

The initial sarcomere length is a critical determinant of muscle function and is regulated by proprioceptors – specialized sensory receptors embedded within muscle tissue, particularly in the muscles of the upper and lower extremities. Proprioceptors relay information concerning muscle length, tension, and movement to the central nervous system, enabling precise neuromuscular control.

Information regarding absolute muscle length and the velocity of length change is primarily provided by muscle spindles, which are arranged in parallel with muscle fibers. Golgi tendon organs (GTOs), located in series with muscle fibers at the musculotendinous junction, detect changes in muscle tension and indirectly contribute to the regulation of muscle length [15]. Muscle spindles contain both dynamic and static components, allowing them to encode both the magnitude and rate of stretch. Rapid elongation of muscle fibers activates the stretch (myotatic) reflex, a protective mechanism that indices reflex muscle contraction to prevent excessive lengthening. In contrast, slow and sustained stretching reduces spindle firing frequency, facilitating accommodation and adaptation to increased muscle length.

During muscle contraction, tension rises within the tendon and is sensed by GTOs, which monitor both the magnitude and rate of tension development. When tension exceeds a certain threshold – serving as a safeguard against structural damage – a reflex inhibition of muscle contraction is initiated through spinal synapses, with modulation by supraspinal centers [16]. Through their coordinated activity, muscle spindled and GTOs play primary central role in protecting the muscle-tendon unit from injury. Proprioceptors also mediate the reciprocal inhibition, whereby activation of an agonist muscle results in reflex relaxation of its antagonist muscle [17].

Muscle responds differently to acute (short-term) and chronic (repeated) stretching. Acute stretching typically produces and immediate increase in ROM, primarily attributable to neural adaptations, including reduced motor neuron excitability, excessive sarcomere elongation, and reorganization of tendons. However, these short-term adaptations are often accompanied by temporary reductions in maximal muscle strength, power output, and muscle endurance [18].

In contrast, chronic stretching – characterized by regular, intensive sessions lasting at least 10 to 15 min-

utes, performed three to four times per week – has been associated with sustained improvements in flexibility, mobility, muscular strength, aerobic endurance. Evidence from animal studies suggests that these adaptations may be partially explained by the addition of sarcomeres in series within muscle fibers, with a process distinct from the parallel sarcomere addition observed during hypertrophy induced by resistance training [19].

During static stretching, tensile force initially acts on the sarcomeres, causing elongation and reduction in overlap between thin and thick myosin filaments, thereby increasing muscle fiber length. Once sarcomeres – and consequently muscle fibers – reach their maximal length, further stretching forces are transmitted to the surrounding connective tissue. This process promotes collagen fiber reorganization, aligning fibers parallel to the direction of applied force [15,20]. The overall increase in muscle length depends on the number of muscle fibers effectively elongated, as individual fibers may respond heterogeneously to the stretching stimulus.

A comprehensive understanding of neuromuscular interactions and adaptive responses during stretching is essential. Stretch-induced elongation of muscle spindles generates afferent signals transmitted to the spinal cord, activating the stretch reflex and opposing further lengthening through reflex contraction. Simultaneously, afferent input is conveyed to higher cortical centers, particularly the insular cortex, where integration of sensory input with emotional, motivational, and cognitive factors occurs. Von Economo neurons play a key role in this process, enabling individuals to tolerate discomfort and sustain stretching [21]. When external force or stretch velocity exceeds the biomechanical and neurogenic capacity of the neuromuscular system – surpassing the so-called "safe zone" – GTO activation predominates. Afferent signals from GTOs inhibit motor neuron activity, overriding spindle-mediated contraction and allowing controlled muscle relaxation. This coordinated activity between the two proprioceptors protects the muscle from injury.

**Static Stretching**

Static stretching (SS) involves elongating a muscle to the point of perceived tension or tolerable discomfort and maintaining this position for a defined duration. From a physiological perspective, SS primarily relies on adaptation and reduced activity of muscle spindles when a muscle is held at an extended length, together with reflex muscle relaxation mediated by activation of GTOs [22,23].

The key advantage of static stretching over other stretching modalities is its capacity to achieve a relatively high stretch intensity through effective isolation of the target muscle group. Consequently, stretching is widely used in both clinical and athletic settings when the primary objectives are to increase joint range of motion and reduce injury risk [2]. Nevertheless, growing evidence suggests that static stretching – particularly when performed for prolonged durations (≥60 seconds) – may adversely affect certain aspects of muscle performance. These findings have important implications for the design of training and rehabilitation programs. Prolonged or excessively intense static stretching has been associated with reductions in strength- and speed-related performance, potentially due to muscle fatigue [19,23,24]. Specifically, SS has been reported to exert a significant negative effect – ranging from -1.2% to -8.5% – across multiple performance parameters, including sprint velocity, jump height, and maximal voluntary contraction of the knee extensors [19,23,25]. In contrast, several studies have reported positive effects of SS on sprint performance, jump height, and peak cycling power [26,27]. Although many of these findings did not reach statistical significance, the frequency of reported positive effects exceeded that of negative effects for measures such as jump height, running speed, and maximal cycling power. Consequently, no clear consensus exists regarding the impact of short-duration static stretching (<60 seconds) on athletic performance, suggesting that individual responsiveness may play a decisive role [19].

With respect to muscle strength, three studies have documented a significant average reduction of approximately 4.2% in eccentric contraction parameters following prolonged static stretching (≥60 seconds), whereas six other studies reported no significant effect. Given that most muscle injuries occur during eccentric contractions, further research is warranted to clarify the influence of static stretching on maximal eccentric strength [19,28].

In the context of the general population and injury prevention, the study by Bandi et al. demonstrated that a minimum of 30 seconds of static stretching is required to elicit a meaningful increase in flexibility [29]. However, evidence suggests that long-term improvements in flexibility are more strongly influenced by stretching frequency than by the duration of individual stretching bouts. In a comprehensive review of stretching modalities, Palma et al. reported that optimal maintenance of flexibility can be achieved with a minimum stretching frequency of five sessions per week and a cumulative stretching duration of approximately 5 minutes per muscle group per week [30].

Finally, Wyone and colleagues showed that so-called micro-stretching – defined as 30-40% of maximal stretch intensity and perceived as mildly uncomfortable – was more effective than conventional static stretching protocols. These findings emphasize the importance of consistency and frequency over

stretch intensity, an approach that may also enhance adherence and long-term compliance in both clinical and athletic populations [31].

**Dynamic Stretching**

Dynamic stretching (DS) consists of controlled, repetitive joint movements performed through the available range of motion, accompanied by a subjective sensation of muscular tension [32]. Several factors support the preferential use of DS over SS during warm-up routines preceding physical activity. First, there is a similarity between stretching and exercise in terms of muscle activation patterns [19,32]. Second, muscle activity during DS increases both core body temperature and local muscle temperature. This rise in temperature accelerates nerve conduction velocity, enhances intracellular enzymatic reactions, boosts metabolism and energy production, and facilitates coordinated muscle action in preparation for specific physical activities [33]. Finally, dynamic movement has been shown to increase activation within central nervous system regions involved in motor control and coordination, in contrast to prolonged SS, which appear to have either neutral or inhibitory effects on these neural centers [34].

Although DS has demonstrated moderate positive effects on muscle function, current evidence does not conclusively support its role in directly enhancing athletic performance. Importantly, however, studies examining DS as part of pre-exercise preparation consistently report an absence of detrimental effects on muscle strength, jump height, or running speed [35,36].

The effects of DS appear to be influenced by both movement frequency and joint-movement amplitude. While some investigations report no significant association between these parameters and performance outcomes, others suggest that meaningful differences exist [2,27,32]. Higher frequencies of DS – and ballistic stretching, which involved momentum-driven movements intended at increase ROM – are associated with increased afferent input from muscle spindles, leading to greater excitation of motor neurons [37]. In this context, DS performed at a frequency of $100 \bullet min^{-1}$ has been shown to elicit significantly greater improvement in vertical jump height (6–9.1%), countermovement jump height (4.9%), quadriceps torque during both eccentric and concentric contractions (7–15%), and knee extensor strength (10.1%) compared with DS performed at $50 \bullet min^{-1}$ [38].

In contrast, Franko et al. reported a negative effect of DS on parameters assessed using the Wingate test, including reduced peak power and a prolonged time to peak power following a DS-based warm-up. These findings may reflect a mismatch between the motor patterns employed during DS exercises and those required for high-intensity cycling, underscoring the importance of movement specificity when designing warm-up protocols [39].

Despite evidence supporting the capacity of DS to increase ROM, relatively few studies have examined the underlying mechanisms responsible for this effect. DS typically involves repeated cycles of muscle loading and unloading over several minutes [32]. The most plausible explanation, extrapolated from animal models, suggests that repetitive muscle elongation elevates intra-fiber and extracellular temperatures, thereby reducing the viscosity of extracellular and intracellular matrix – referred to as the thixotropic effect [40]. This reduction in tissue viscosity may facilitate decreased muscle stiffness and enhanced ROM in humans [41].

**Discussion**

There remains considerable debate regarding two commonly attributed benefits of flexibility: injury prevention and enhancement of athletic performance. Although stretching is widely regarded as a preventive measure against athletic injuries, epidemiological evidence supporting this assumption remains limited [42]. Interestingly, earlier theories suggested that a certain degree of muscle stiffness might confer a protective effect by enabling more efficient load distribution across static and dynamic stabilizing structures during joint stress [43]. Conversely, hypermobility or excessive stretching may theoretically increase mechanical stress on ligaments, osseous structures, and articular cartilage, potentially leading to injury or degenerative changes over time. In line with this hypothesis, the main risk factors for joint injury include a history of previous injury and the presence of joint hypermobility.

At present, the role of pre-exercise stretching in injury prevention remains inconclusive. To address this uncertainty, the American College of Sports Medicine (ACSM) supported a systematic review conducted by Taker and colleagues; however, the authors found insufficient evidence to confirm a protective effect of routine stretching on injury incidence [42,44]. More recently, Takeuchi et al. [45] concluded in 2024 literature review that static stretching reduces the risk of muscle injuries but has no significant effect on ligament injuries. Other studies corroborate a reduced incidence of muscle injuries while simultaneously reporting an increased risk of bone and joint injuries [46].

With respect to athletic performance, several laboratory studies have demonstrated that less flexible runners exhibited lower oxygen consumption at a given speed and distance compared to their more flexible counterparts [47]. A 2025 systematic review by Warneke et al. [48] reported that prolonged static stretching (>60 seconds) immediately before strength testing or ath-

letic performance results in an acute reduction in force production. The authors further suggest that combining short-duration static stretching with dynamic stretching during warm-up may increase joint ROM while minimizing strength deficits. In a subsequent publication, Warneke et al. [49] reported limited evidence that chronic static stretching (≥15 minutes, ≥6 weeks, ≥5 sessions per week) can increase maximal strength and muscle size, although the underlying physiological mechanisms remain unclear. Notably, this approach may be particularly valuable in older adults when traditional resistance training is contraindicated.

Another important consideration concerns the sequencing and scheduling of different exercise modalities. Systematic reviews and meta-analyses indicate that optimal therapeutic exercise programs typically emphasize a single primary exercise type – whether aerobic, flexibility-based, or strength training. This recommendation is based on divergent molecular adaptations, as aerobic and resistance exercises stimulate mitochondrial biogenesis and myofibrillar protein synthesis, respectively. Concurrent training appears to attenuate the molecular response to each stimulus. Extrapolating from this concept, stretching could theoretically be performed in a separate training session; however, no current guidelines or empirical studies have evaluated the efficacy of such an approach.

Finally, challenges remain regarding the timing of stretching relative to therapeutic exercises goals. Questions persist concerning the influence of proprioceptive inhibition on motor learning and the potential effects of stretching when incorporated before or after physiotherapy sessions, particularly in the context of neurologic rehabilitation.

## Conclusion

At present, no consensus exists regarding the necessity of stretching or its definitive role in injury prevention. Nevertheless, the psychological benefits of stretching – particularly its capacity to reduce perceived muscle tension and mental stress – should not be underestimated. Clinicians and sports professionals should therefore individualize stretching protocols according to therapeutic objectives, injury risk, and performance demands. Research suggests meaningful distinctions between the effects of acute and chronic stretching. Acute stretching may reduce the risk of muscle strains in individuals with excessive muscle tension, whereas those with optimal muscle tone appear to derive minimal preventive benefit. Individuals with inherently greater flexibility tend to be less susceptible to exercise-related injuries, and acquired flexibility can be increased through intensive stretching programs performed three or four times per week. Owing to these differences, many experts currently advocate performing the majority of stretching at the end of training sessions rather than beforehand. As with most interventions in medicine and exercise science, no single stretching strategy is universally applicable. Optimal outcomes depend on individualized assessment, appropriate timing, and clearly defined therapeutic or performance-related goals.

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Rad je primljen 5. XII 2025.
Recenziran 12. I 2026.
Prihvaćen za štampu 12. I 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:278-283.

# ANESTHESIA IN CHILDREN WITH ANTERIOR MEDIASTINAL MASSES – ANESTHETIC ALGORITHM AND PERIOPERATIVE CONSIDERATIONS

# *ANESTEZIJA KOD DECE SA PATOLOŠKIM MASAMA U PREDNJEM MEDIJASTINUMU – ANESTEZIOLOŠKI ALGORITAM I PERIOPERATIVNA RAZMATRANJA*

**Anna URAM BENKA[1,2], Izabella FABRI GALAMBOŠ[1,2], Nikola BOŠKOVIĆ[1,2], Dragan TURANJANIN[1,2], Nemanja GALETIĆ[2] and Jasminka URAM DUBOVSKI[3]**

ORCID NUMBER
Anna Uram Benka – 0000-0002-2815-017X
Izabella Fabri Galamboš – 0000-0001-5032-671X
Nikola Bošković – 0000-0002-6316-4120
Dragan Turanjanin – 0009-0002-9638-0935
Nemanja Galetić – 0009-0004-2022-5431
Jasminka Uram Dubovski – 0000-0001-9442-6480

University of Novi Sad, Faculty of Medicine Novi Sad[1]
Institute of Children and Youth Health Care of Vojvodina, Novi Sad[2]
University Clinical Center of Vojvodina, Novi Sad
Clinic for Gynecology and Obstetrics[3]

Review article
*Pregledni članak*
UDK 616.27-006-053.2:616-089.5
https://doi.org/10.2298/MPNS2512284U

**Abstract**

**Introduction.** Mediastinal masses in children encompass a broad spectrum of histopathological and radiological entities. **Anatomy and Physiology.** The mediastinum is traditionally divided into three compartments, without discrete anatomical barriers between them, allowing lesions to extend across compartments. Physiological compromise results primarily from compression of the airway, heart, or major vessels. **Signs and Symptoms.** Clinical presentation varies widely depending on the size, location, and growth rate of the mass. **Preoperative Testing.** Preoperative evaluation typically includes radiography, contrast-enhanced computed tomography, pulmonary function testing, and transthoracic echocardiography. **Anesthetic Management and Procedure Location.** Operative procedures should be performed in an operating room. In extremely high-risk cases, extracorporeal bypass may be considered. **Monitoring and Vascular Access.** Large-bore intravenous access should be secured. Arterial monitoring may be required for continuous hemodynamic assessment. **Anesthetic Technique.** Anesthetic techniques include local, regional and general anesthesia. In many cases, general anesthesia is unavoidable. Inhalational induction with sevoflurane is commonly employed in pediatric patients. **Management of Intraoperative Complications.** In the event of impaired ventilation, management strategies include increasing inspired oxygen concentration, applying continuous positive airway pressure, and advancing the endotracheal tube distal to the site of obstruction. In cases of cardiovascular collapse, immediate interventions include rapid intravenous fluid administration and reduction of anesthetic depth. **Postoperative care.** Early communication with the intensive care unit is recommended when complications are anticipated. Extubation should be performed only when the child is fully awake. **Conclusion.** Comprehensive preoperative evaluation is essential to assess cardiopulmonary compromise and ensure safe anesthetic management in children undergoing diagnostic or surgical procedures.

**Key words:** Mediastinal Neoplasms; Lymphoma; Child; Anesthesia, General; Sevoflurane; Tomography, X-Ray Computed; Cardiopulmonary Bypass; Intraoperative Complications; Perioperative Care

**Sažetak**

**Uvod**. Medijastinalne mase obuhvataju širok spektar histopatoloških i radioloških entiteta. **Anatomija i fiziologija.** Medijastinum je podeljen na tri dela, pri čemu tumorske promene mogu da se nesmetano šire iz jednog dela ka ostalim. Kardiorespiratorne komplikacije se najčešće razvijaju usled kompresije disajnih puteva, srca ili glavnih krvnih sudova. **Znaci i simptomi.** Kod dece se javlja širok spektar znakova i simptoma, na koje utiču veličina, lokacija i brzina rasta tumora. **Preoperativna dijagnostika.** Preoperativna dijagnostika obuhvata rendgen grudnog koša, kompjuterizovanu tomografiju sa kontrastom, testove plućne funkcije i ehokardiografiju. **Operativne procedure.** Operativne procedure treba izvoditi u operacionoj sali. Kod visokorizičkih bolesnika, može se razmotriti primena ekstrakorporalne membranske oksigenacije. **Monitoring i vaskularni pristup.** Neophodno je plasirati intravenske braunile što većeg promera pre plasnirane hirurške procedure. Kod hemodinamički nestabilnih bolesnika, potrebno je plasirati arterijsku kanilu. **Tehnika anestezije.** Tehnike anestezije uključuju lokalnu, regionalnu i opštu anesteziju. U brojnim slučajevima, opšta anestezija je metoda izbora. Indukcija sevofluranom se često koristi kod dece. **Lečenje intraoperativnih komplikacija.** Kod nezadovoljavajuće ventilacije, pojedine tehnike modifikovanja parametara ventilacije jesu: povećanje inspiratorne koncentracije kiseonika, primena kontinuiranog pozitivnog pritiska u disajnim putevima i plasiranje endotrahealnog tubusa distalno od mesta opstrukcije disajnog puta tumorskom promenom. U slučaju kardiovaskularnog kolapsa, neophodno je ordinirati intravenski bolus tečnosti i smanjiti dubinu anestezije. **Postoperativna nega.** Ukoliko se očekuje ili dolazi do komplikacija, treba obezbediti mesto u jedinici intenzivnog lečenja. Ukoliko je moguće, dete treba probuditi i ekstubirati na kraju operativnog zahvata. **Zaključak.** Sveobuhvatna preoperativna evaluacija je neophodna za procenu kardiopulmonalne kompromitovanosti i bezbedno izvođenje dijagnostičkih i hirurških intervencija u anesteziji.

**Ključne reči:** medijastinalni tumori; limfomi; deca; opšta anestezija; sevoflurane; CT; kardiopulmonalni bajpas; intraoperativne komplikacije; perioperativna nega

✉ Corresponding author: Dragan Turanjanin, E-mail: dragan.turanjanin@mf.uns.ac.rs, ana.uram-benka@mf.uns.ac.rs

***Abbreviations***

AMMs – anterior mediastinal masses
SVC – superior vena cava
CT – computed tomography
ECHO – echocardiography
GA – general anesthesia
CPAP – continuous positive airway pressure
PEEP – positive end-expiratory pressure
IV – intravenous
ECMO – extracorporeal membrane oxygenation

## Introduction

Mediastinal masses encompass a broad spectrum of histopathological and radiological entities. Common types in pediatric patients include lymphomas, thymomas, neurogenic tumors, and benign cysts, which together account for approximately 60% of cases [1]. Despite their clinical significance, there is a lack of high-quality evidence in the literature to guide risk stratification and operative planning for the safe administration of anesthesia and surgery in children with anterior mediastinal masses (AMMs) [2]. Managing children with AMMs is particularly challenging because of the risk of severe cardiopulmonary compromise, which may be exacerbated under general anesthesia [1].

### Anatomy and Physiology

The mediastinum is divided into three compartments: anterior (with superior and inferior subdivisions), middle, and posterior. Although these compartments are identifiable on chest radiographs, no discrete anatomical planes separate them, and masses may extend across compartments. The heart and great vessels, tracheobronchial tree, esophagus, nerves, thymus, and lymphatic structures are all located within this confined space [2]. Anterior mediastinal masses pose the greatest perioperative risk, especially in children, where they are most commonly encountered. Lymphoma represents the most frequent cause of AMMs in pediatric patients [3].

Physiological compromise arises primarily from compression of the airway, heart, or major vessels. The mass may compress the right cardiac chambers, superior vena cava (SVC), pulmonary arteries, or pulmonary veins, leading to decreased cardiac output and right ventricular failure. Clinical manifestations of cardiac compression include syncope, tachycardia, jugular venous distension, SVC syndrome, and cyanosis [4]. Pulmonary artery compression may result in hypoxemia, hypoventilation, and right ventricular strain. Compression of the trachea or bronchi contributes to respiratory distress, manifesting as dyspnea, cough, and stridor [5].

Positioning and anesthetic depth significantly influence pathophysiology. The supine position increases intrathoracic pressure due to cephalad displacement of the diaphragm, exacerbating airway and vascular compression. These effects are amplified under general anesthesia due to airway smooth muscle relaxation and reduced airway tone – factors particularly relevant in children, whose airways are more collapsible. Maintaining spontaneous ventilation can mitigate compression, whereas positive pressure ventilation may worsen airway or vascular collapse. Neuromuscular blockade further reduces chest wall tone and increases the risk of complete airway obstruction.

### Signs and Symptoms

Children with AMMs may present with a wide range of symptoms depending on the size, location, and growth rate of the mass. Compared with adults, pediatric patients more commonly exhibit rapidly growing and frequent malignant tumors that compress relatively softer airways and vascular structures. Preoperative anesthetic assessment should focus on identifying features associated with increased perioperative risk. Evidence suggests that tracheal or vascular compression and respiratory symptoms – such as cough, dyspnea, and stridor – are associated with higher perioperative complication rates [6,7]. However, similar symptoms may also occur in pneumothorax or pneumomediastinum and should be considered in the differential diagnosis [8]. The incidence of perioperative complications ranges from 9% to 20% based on single-institution case series. A retrospective 8-year review reported that 76% of children presenting with AMMs were symptomatic at diagnosis [2].

### Preoperative Testing

Diagnosis is often initially made on chest radiography. The mediastinal mass ratio has been used for risk stratification [2]. An average mediastinal mass ratio of 0.56 was reported in children who experienced perioperative complications, suggesting that larger masses may confer greater risk [9]. Key preoperative investigations include:

– Contrast-enhanced computed tomography (CT): Provides essential information regarding mass location and the degree of airway or vascular compression. CT allows measurement of the tracheal cross-sectional area at its narrowest point; smaller areas correlate with increased perioperative risk [2].

– Pulmonary function testing: May aid in risk stratification but is often difficult to perform reliably in young children.

– Transthoracic echocardiography (ECHO): Assesses cardiac compromise, including pericardial effusion, or tamponade, which significantly increases perioperative risk [10,11].

It is important to note that echocardiographic assessment is performed in awake children; therefore, the hemodynamic effects of anesthetic agents may not be fully appreciated preoperatively [2].

**Anesthetic Management and Procedure Location**

Management requires a multidisciplinary approach involving oncology, anesthesiology, radiology, surgery, and critical care teams. Coordination is essential, particularly when balancing the urgency of obtaining a tissue diagnosis with patient safety. In selected high-risk patients, preoperative corticosteroid therapy may reduce airway compromise prior to biopsy [10].

Procedures should ideally be performed in the main operating room, where experienced personnel, advanced airway equipment, and cardiopulmonary bypass support are readily available. In extremely high-risk cases, extracorporeal bypass may be considered, although cannulation is technically more challenging in pediatric patients [2,12].

**Monitoring and Vascular Access**

Large-bore intravenous access should be established in both upper and lower extremities, particularly in patients with suspected SVC syndrome. Arterial catheterization may be indicated for continuous hemodynamic monitoring depending on the patient's clinical condition.

**Anesthetic Technique**

***Local Anesthesia***

Obtaining tissue samples under local anesthesia is feasible in adults but often impractical in young children due to anxiety, poor cooperation, and potential airway compromise. Older, cooperative children may tolerate superficial lymph node biopsy under local anesthesia. More invasive procedures such as mediastinoscopy or awake fiberoptic intubation are generally not feasible.

***Sedation and Regional Anesthesia***

Sedation may facilitate biopsy in children who cannot tolerate local anesthesia alone. Preferred agents include dexmedetomidine and ketamine, as they preserve respiratory drive. Ketamine provides sympathomimetic support, helping maintain hemodynamic stability. Midazolam (0.1 mg/kg) may reduce ketamine-related psychotropic effects. Glycopyrrolate (10 mcg/kg) may be used as antisialagogue.

Suggested dosing:

– Dexmedetomidine: 1 mcg/kg loading dose over 10 minutes, followed by 0.25–2 mcg/kg/h infusion

– Ketamine: 1–2 mg/kg bolus over 2 minutes, with additional 0.5 mg/kg increments as needed

Regional techniques may assist in selected older children but are limited by cooperation and potential coagulopathy related to malignancy. Even under sedation, airway compromise may persist.

***General Anesthesia***

General anesthesia (GA) is often unavoidable. Intravenous access should be secured before induction whenever possible. Techniques preserving spontaneous ventilation are preferred to maintain airway tone and prevent dynamic collapse.

Inhalational induction with sevoflurane is commonly employed. Alternatively, intravenous induction with propofol - while maintaining spontaneous ventilation - may be performed by experienced pediatric anesthesiologists. Extreme caution is required, as apnea may result in inability to ventilate, intubate, or re-establish a patent airway.

If an unexpected AMM is discovered during induction for an unrelated procedure, immediate assistance should be summoned, neuromuscular blockade reversed if feasible, and anesthetic depth reduced to restore spontaneous ventilation [13–19].

**Management of Intraoperative Complications**

***Respiratory Collapse***

Immediate intervention is required if ventilation becomes impaired:

– Increase $FiO_2$

– Apply CPAP to splint airways and restore functional residual capacity

– Reposition (lateral or prone if necessary) to relieve compression

– Attempt positive pressure ventilation with PEEP

– Advance the endotracheal tube distal to the obstruction

– Consider one-lung ventilation for distal obstruction

A rigid bronchoscope should be immediately available to bypass obstruction and ventilate distal airways. CPAP may be delivered via a Mapleson F circuit attached to the bronchoscope, though air trapping must be considered. Heliox may temporarily reduce airway resistance but is limited in hypoxic emergencies due to reduced oxygen concentration.

***Cardiovascular Collapse***

Initial management includes:

– Rapid intravenous fluid bolus

– Reduction of anesthetic depth

– Repositioning (including prone positioning if beneficial)

If instability persists, emergent sternotomy with manual elevation of the mass from central mediastinal structures may be necessary. Respiratory and cardiovascular compromise are frequently interrelated; optimization of one system may improve the other [15,16,18].

Extracorporeal membrane oxygenation (ECMO) may be considered preemptively in extremely high-risk patients or as rescue therapy, although cannulation in is technically challenging and profound hypoxia may occur during setup [13,17].

**Postoperative Care**

Postoperative disposition depends on preoperative symptoms, intraoperative events, and residual mass effect. Early communication with the intensive care unit is recommended when complications are anticipated. Ideally, the child should be fully awake and extubated at the conclusion of surgery. If significant mass effect persists, enhanced postoperative monitoring is required. Even after mass removal, vigilance for bleeding or airway edema is essential [20].

**Conclusion**

Children with anterior mediastinal masses present significant anesthetic challenges. Comprehensive preoperative evaluation – including detailed history, imaging, and echocardiography – is essential for assessing cardiopulmonary compromise. Effective multidisciplinary communication, careful procedural planning, and individualized anesthetic strategies are critical for optimizing perioperative safety. Maintaining spontaneous ventilation when feasible, minimizing neuromuscular blockade, and preparing for emergent airway or cardiovascular intervention remain cornerstone principles in the management of these high-risk patients.

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Rad je primljen 8. II 2026.
Recenziran 18. II 2026.
Prihvaćen za štampu 18. II 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:284-287.

Med Pregl 2025; LXXVIII (9-12): 289-293. Novi Sad: septembar-decembar.



# WHEN SECONDS COUNT – ETHICAL AND EVIDENCE-BASED MANAGEMENT OF NEUROSURGICAL EMERGENCIES IN PREGNANCY

# *KADA SEKUNDE ODLUČUJU – ETIČKO I NA DOKAZIMA ZASNOVANO ZBRINJAVANJE NEUROHIRURŠKIH HITNIH STANJA U TRUDNOĆI*

**Jovana RODIĆ[1], Dušan RODIĆ[2,3], Dušica PEROVIĆ[4], Sara ĐURICA[1], Luka TUCAKOV[5] and Sara AZARIĆ[6]**

ORCID NUMBER
Jovana Rodić – 0009-0006-0669-771X
Dušan Rodić – 0009-0007-2911-6217
Dušica Perović – 0000-0002-8206-351X
Sara Đurica – 0009-0003-6514-948X
Luka Tucakov – 0009-0004-3621-5078
Sara Azarić – 0009-0008-8773-5785

University Clinical Center of Vojvodina, Clinic for Gynecology and Obstetrics, Novi Sad[1]
Clinic for Neurosurgery, Novi Sad[2]
University of Novi Sad, Faculty of Medicine Novi Sad, Department for Surgery[3]
Rehabilitation Clinic "Wellness studio Laser", Vrbas[4]
University Clinical Center of Vojvodina, Clinic for Maxillofacial Surgery, Novi Sad[5]
University of Novi Sad, Faculty of Medicine Novi Sad[6]

Seminar in medicine
*Seminar iz medicine*
UDK 616.8-001-083.98:618.231
UDK 614.253
https://doi.org/10.2298/MPNS2512289R

**Abstract**

**Introduction.** Neurosurgical emergencies during pregnancy are associated with maternal and fetal risk and require rapid, coordinated, and ethically sound decision-making. Conditions such as traumatic brain injury, intracranial hemorrhage, rapidly expanding intracranial tumors, acute hydrocephalus, and spinal cord compression often necessitate urgent intervention despite the physiological adaptations of pregnancy, altered pharmacokinetics, anesthetic constraints, and limitations in diagnostic imaging. Owing to the predominance of case reports and small series in the literature, management strategies are frequently individualized. **Material and Methods.** This narrative review synthesizes the available literature on urgent neurosurgical care in pregnant patients, with particular emphasis on maternal and fetal outcomes, pregnancy-specific modifications of neurocritical and surgical management, and ethical considerations. A structured search of PubMed and Scopus was conducted to identify relevant studies addressing surgical timing, perioperative strategies, multidisciplinary coordination, and reported ethical dilemmas. **Conclusion.** The reviewed evidence underscores the importance of early diagnosis, prioritization of maternal stabilization, and close collaboration among neurosurgery, obstetrics, anesthesia, and neonatology teams. When indicated, neurosurgical procedures should generally not be delayed solely due to pregnancy, and individualized anesthetic strategies may help minimize fetal exposure. Ethical issues – including informed consent, maternal autonomy, and consideration of fetal interests – require clear communication and shared decision-making. Despite improvements in care, standardized management guidelines remain limited, highlighting the need for higher-quality evidence and structured interdisciplinary treatment pathways.

**Key words:** Pregnancy; Brain Injuries, Traumatic; Intracranial Hemorrhages; Neurosurgical Procedures; Patient Care Team; Ethical Dilemmas

**Sažetak**

**Uvod.** Neurohirurška hitna stanja tokom trudnoće nose visok rizik za majku i fetus i zahtevaju brzo, koordinisano i etički utemeljeno donošenje odluka. Stanja poput traumatske povrede mozga, intrakranijalnog krvarenja, brzorastućih tumora, akutnog hidrocefalusa i kompresije kičmene moždine zahtevaju pravovremenu intervenciju, uprkos izazovima koje nameću fiziološke promene trudnoće, izmenjena farmakokinetika, ograničenja u primeni anestetika i smanjene dijagnostičke mogućnosti. Pošto se većina dostupnih dokaza zasniva na prikazima slučajeva i manjim serijama slučajeva, postupanje se često prilagođava svakoj pojedinačnoj pacijentkinji. **Materijal i metode.** Ovaj rad obuhvata postojeću literaturu o urgentnoj neurohirurškoj nezi kod trudnica, sa fokusom na ishode za majku i fetus, specifične modifikacije neurokritične i hirurške nege, kao i etičke aspekte. Strukturisano pretraživanje naučnih baza *PubMed* i *Scopus* identifikovala je studije o hirurškom tajmingu, perioperativnim strategijama, multidisciplinarnoj koordinaciji i zabeleženim etičkim dilemama. **Zaključak.** Ključni rezultati ističu značaj rane dijagnostike, stabilizacije majke i bliske saradnje neurohirurga, ginekologa-akušera, anesteziologa i neonatologa. Neophodne hirurške intervencije, po pravilu, ne treba odlagati zbog trudnoće, a prilagođene anestetičke strategije mogu smanjiti fetalnu izloženost lekovima. Etička pitanja – uključujući informtivni pristanak, autonomiju majke i interese fetusa – zahtevaju jasnu komunikaciju. Uprkos napretku, standardizovane smernice ostaju ograničene, što naglašava potrebu za jačim dokazima i strukturisanim interdisciplinarnim pristupom.

**Ključne reči:** trudnoća; traumatske povrede mozga; intrakranijalno krvarenje; neurohirurške procedure; multidisciplinarni tim; etičke dileme

✉ Corresponding author: Jovana Rodić, E-mail: 965jovana@gmail.com, dusan.rodic@mf.uns.ac.rs

***Abbreviations***
TBI – traumatic brain injury
MRI – magnetic resonance imaging
CT – computed tomography

## Introduction

Neurosurgical emergencies in pregnancy represent a high-risk clinical domain in the intersection of acute neurocritical care and maternal–fetal medicine. These conditions are associated with disproportionate maternal and perinatal morbidity and mortality due to the concurrence of rapidly progressive neurological compromise and the complex physiological adaptations of gestation. Clinical management is further complicated by diagnostic and therapeutic limitations, variability in institutional expertise, and a scarcity of high-quality evidence. As a result, optimal outcomes depend on early recognition, prompt intervention, and coordinated multidisciplinary care, with treatment strategies carefully individualized to balance maternal stabilization with fetal safety. The continued reliance on case reports and expert consensus highlights the lack of structured, evidence-informed frameworks applicable to these uniquely challenging scenarios [1–12]. The clinical spectrum encompasses a heterogeneous group of acute, potentially life-threatening conditions, including intracranial and subarachnoid hemorrhage, traumatic brain injury (TBI), rapidly expanding intra-axial and extra-axial mass lesions, acute hydrocephalus, spinal cord compression syndromes, and other cases of sudden neurological deterioration. Although relatively uncommon, these entities are associated with substantial maternal morbidity and increased perinatal vulnerability, often exacerbated by diagnostic delays, concerns regarding fetal exposure to imaging modalities, and hesitancy to pursue timely invasive interventions [2,3,7,10].

Pregnancy-related physiological changes – such as altered cerebrovascular reactivity, increased intravascular volume, gestation-specific modifications in coagulation and hemostasis, reduced functional residual capacity, and significant alterations in pharmacokinetics and anesthetic sensitivity – further complicate the application of standard neurocritical and neurosurgical algorithms. These adaptations necessitate recalibration of monitoring strategies, neuroprotective measures, surgical timing, and anesthetic management to mitigate risks to both maternal neurological function and fetal viability [4,12]. Beyond clinical and physiological complexity, neurosurgical emergencies in pregnancy raise profound ethical challenges. Decision-making may be influenced by maternal-fetal risk asymmetry, particularly when urgent intervention carries uncertain fetal consequences or when gestational age affects neonatal viability, the feasibility of perimortem delivery, or therapeutic aggressiveness. In the absence of comprehensive guidelines and robust prospective data, clinicians must rely on multidisciplinary deliberation, structured ethical analysis, and transparent patient counseling to guide management [1,5,8,9]. The convergence of neurological urgency, physiological vulnerability, and ethical uncertainty underscores the need for comprehensive, evidence-informed approaches integrating emergent neurosurgical priorities with maternal-fetal considerations.

## Material and Methods

This review aims to synthesize current evidence and expert consensus regarding neurosurgical emergencies during pregnancy, identifying gestation-specific physiological, diagnostic, anesthetic, and therapeutic factors requiring modification of standard neurosurgical practice, and examine prevailing ethical challenges and multidisciplinary decision-making frameworks.

A structured literature review was conducted using the PubMed and Scopus databases, identifying relevant publications available up to the time of writing. Search terms included combinations of "neurosurgical emergencies", "pregnancy", "intracranial hemorrhage", "traumatic brain injury", "spinal lesions", "neurocritical care", "maternal outcomes", and "ethical considerations". Original research articles, systematic reviews, narrative reviews and case series were included.

Eligibility criteria encompassed studies addressing urgent neurosurgical interventions in pregnant patients, reporting maternal or fetal outcomes, or discussing ethical and clinical decision-making processes. Exclusion criteria included non-acute neurosurgical conditions, non-human studies, and reports lacking sufficient clinical or methodological detail. Studies from both low- and high-resource settings were included to reflect variability in institutional capabilities and practice patterns.

Data extraction focused on maternal and fetal morbidity and mortality, timing and type of neurosurgical intervention, anesthetic strategies, multidisciplinary coordination, and documented ethical dilemmas. The extracted evidence was synthesized to identify core principles guiding clinical practice, emphasizing pregnant-specific physiologic considerations, perioperative risk mitigation, and evidence-informed, ethically grounded decision-making. Where available, consensus statements and institutional protocols were incorporated to provide a structured framework applicable across diverse clinical environments.

## Discussion

Neurosurgical emergencies during pregnancy constitute rare but high-stakes clinical situations in which acute neurological deterioration threatens both maternal and fetal survival. Conditions such as traumatic brain injury (TBI), intracranial hemorrhage, rapidly expanding intracranial tumors, and other fulminant neurosurgical pathologies require urgent intervention to prevent maternal morbidity and mortality, while simultaneously accounting for fetal well-being [1,2]. The complexity of management arises from pregnancy-related physiological adaptations, altered pharmacodynamics, anesthetic constraints, and the necessity for rapid multidisciplinary coordination [3,4].

Although uncommon, these emergencies carry profound consequences. Esmaeilzadeh et al. [1] reported that prompt diagnosis and timely neurosurgical intervention are essential for optimizing maternal outcomes without necessarily compromising fetal viability. Severe TBI during pregnancy exemplifies the dual-patient challenge, wherein life-saving maternal interventions may entail unavoidable fetal risk [2,3]. Ethical dilemmas frequently arise when maternal and fetal interests appear discordant, necessitating careful application of ethical principles such as autonomy, beneficence, and non-maleficence. Physiological adaptations of pregnancy complicate both diagnostic evaluation and therapeutic planning [4]. Magnetic resonance imaging (MRI) is generally preferred for neuroimaging due to the absence of ionizing radiation, while computed tomography (CT) remains justified in emergent situations requiring rapid assessment [3,5]. Importantly, the literature consistently indicates that necessary neurosurgical procedures, including craniotomy and tumor resection, should not be delayed solely because of pregnancy, as postponement is associated with worse maternal outcomes [5,6]. Anesthetic management must be carefully tailored, following neuroanesthetic principles adapted to pregnancy-specific physiological constraints [4]. Multidisciplinary collaboration is repeatedly emphasized as a determinant of favorable

**Table 1.** Key neurosurgical emergencies during pregnancy

| Condition | Clinical presentation | Diagnostic limitations in pregnancy | Therapeutic priorities | Perioperative considerations | Expected outcomes |
|---|---|---|---|---|---|
| Traumatic brain injury (TBI) | Altered consciousness, focal neurological deficit, raised intracranial pressure; often associated with polytrauma | Limited use of CT due to radiation concerns; MRI preferred when feasible; fetal monitoring may interfere with acute imaging | Rapid maternal stabilization, airway protection, control of intracranial pressure; neurosurgical intervention when indicated | Multidisciplinary trauma management; left lateral positioning to avoid aortocaval compression; cautious use of sedatives and osmotherapy | Maternal outcome depends on injury severity; fetal outcome closely linked to maternal hemodynamic stability |
| Intracranial hemorrhage (ICH) | Sudden headache, focal deficit, decreased level of consciousness; may be associated with hypertension or coagulopathy | CT often required in emergencies despite radiation exposure; MRI useful for etiological assessment | Immediate blood pressure control, reversal of coagulopathy, urgent neurosurgical evacuation when indicated | Tight hemodynamic control; avoidance of hypotension and hypoxia; fetal monitoring in viable gestation | Favorable outcomes possible with timely intervention; delays increase maternal and fetal mortality |
| Intracranial tumors | Progressive neurological deficits, seizures, signs of raised intracranial pressure; symptom progression may accelerate during pregnancy | MRI without contrast preferred; gadolinium generally avoided; limited role of CT | Symptom control; surgical resection if neurological deterioration occurs; elective surgery deferred when stable | Timing of surgery individualized by gestational age and tumor behavior; anesthetic strategies minimizing fetal exposure | Generally good maternal outcomes with appropriate timing; fetal outcomes favorable when maternal stability maintained |
| Acute hydrocephalus | Headache, nausea, vomiting, altered mental status, papilledema | MRI preferred; rapid imaging essential despite pregnancy | Urgent cerebrospinal fluid diversion (EVD or shunt) | Careful fluid and electrolyte balance; infection prevention; coordination with obstetric team | Good maternal and fetal outcomes when treated promptly |
| Spinal stenosis/ cord compression | Progressive motor weakness, sensory loss, sphincter dysfunction | MRI is modality of choice; diagnostic delay may occur due to nonspecific symptoms | Urgent decompression in cases of neurological deterioration | Prone positioning challenges; gestational age–specific anesthetic planning | Neurological recovery depends on timing of intervention; fetal outcomes generally favorable |

outcomes. Cohen-Gadol et al. [5] demonstrated improved results when neurosurgeons, obstetricians, anesthesiologists, and neonatologists jointly determined the timing and extent of intervention. Maternal stabilization remains the primary priority, with fetal considerations informing perioperative planning than delaying essential treatment [3,7]. Established guidelines for management of pregnant trauma patients emphasize structured protocols that integrate ethical deliberation with clinical urgency. In the absence of an immediate threat to maternal life or evidence of a rapidly progressive neurological deterioration, deferring surgery until the postpartum period is generally appropriate. Conversely, when operative intervention is clearly indicated, it should not be delayed because of pregnancy, as maternal safety remains the overriding priority. Elective or non-urgent procedures are optimally scheduled during the second trimester, when the risks of miscarriage and preterm labor are lowest, whereas in early pregnancy patients can often be managed similarly to non-pregnant individuals [7].

Ethicolegal considerations further complicate urgent decision-making. Informed consent must address potential maternal and fetal risks under time-critical conditions, while jurisdiction differences in maternal autonomy and fetal rights influence clinical and legal responsibility. Comprehensive documentation of ethical reasoning and risk-benefit assessment is therefore essential [8]. Emerging strategies, such as awake craniotomy in selected pregnant patients, have demonstrated feasibility and may reduce fetal exposure to anesthetic agents while allowing real-time neurological assessment [10]. Similarly, evidence from intracranial hemorrhage and TBI case series suggest that timely, evidence-based intervention can yield favorable maternal and neonatal outcomes when guided by structured neurocritical care protocols adapted for pregnancy [11,12]. Collectively, these observations underscore the need for structured, ethically grounded, and evidence-based clinical pathways capable of addressing the inherent dual-patient complexity of neurosurgical emergencies during pregnancy **(Table 1).** Despite advances in clinical management, significant gaps remain in the development of standardized guidelines for pregnant patients requiring urgent neurosurgical care. Many current recommendations are derived from case reports or extrapolations from non-pregnant populations, highlighting the need for multicenter prospective studies and registries to generate robust data [6,9]. Ethical dilemmas, legal constraints, and logistical challenges in acute care settings further hinder standardization. Nevertheless, the integration of contemporary evidence with ethical frameworks and close multidisciplinary collaboration remains the most reliable strategy for optimizing both maternal and fetal outcomes.

## Conclusion

Neurosurgical emergencies during pregnancy require rapid, individualized, and ethically grounded decision-making within a multidisciplinary team. Clinicians must navigate dual responsibilities toward both mother and fetus, guided by evolving evidence, expert consensus, and jurisdiction-specific ethical and legal frameworks. Continued research is essential to establish standardized guidelines capable of optimizing outcomes in these high-risk clinical scenarios.

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Rad je primljen 4. XII 2025.
Recenziran 2. II 2026.
Prihvaćen za štampu 2. II 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:289-293.

Med Pregl 2025; LXXVIII (9-12): 295-299. Novi Sad: septembar-decembar.

# CASE REPORTS
# *PRIKAZI SLUČAJEVA*

## ISOLATED ORBITAL RELAPSE OF FOLLICULAR LYMPHOMA DETECTED BY 18F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY WITH COMPUTED TOMOGRAPHY – A CASE REPORT

## *IZOLOVANI ORBITALNI RELAPS FOLIKULARNOG LIMFOMA DETEKTOVAN 18F-FLUORODEOKSIGLUKOZNOM POZITRONSKOM EMISIONOM TOMOGRAFIJOM SA KOMPJUTERIZOVANOM TOMOGRAFIJOM – PRIKAZ SLUČAJA*

**Milica KOTUR[1], Nikola PANTIĆ[1], Strahinja ODALOVIĆ[1,2], Jelena PANTOVIĆ[1], Dragana ŠOBIĆ ŠARANOVIĆ[1,2] and Vera ARTIKO[1,2]**

ORCID NUMBER
Milica Kotur - 0009-0001-7713-9364
Nikola Pantić - 0009-0006-6070-0828
Strahinja Odalović - 0000-0002-1615-5379
Jelena Pantović - 0000-0001-7013-8484
Dragana Šobić Šaranović - 0000-0001-9600-090X
Vera Artiko - 0000-0002-6078-4500

University Clinical Center of Serbia, Belgrade
Center for Nuclear Medicine with PET[1]
University of Belgrade, Faculty of Medicine, Belgrade[2]

Case report
*Prikaz slučaja*
UDK 617.7-006.44-073.7:616-08
https://doi.org/10.2298/MPNS2512295K

**Abstract**

**Introduction**. Orbital localization of follicular lymphoma is exceedingly rare, and its diagnosis is often challenged due to a broad spectrum of ophthalmic differential diagnoses. We report a case of orbital relapse of follicular lymphoma detected five years after complete remission using 18F-fluorodeoxyglucose positron emission tomography with computed tomography. **Case Report.** A 53-year-old man diagnosed with follicular lymphoma in 2013 achieved complete remission following chemotherapy in 2017 and remained under routine follow-up for the subsequent five years. In 2022, he presented with a 10-day history of right orbital pain. Clinical examination revealed right-sided exophthalmos and eyelid ptosis. 18F-fluorodeoxyglucose positron emission tomography with computed tomography demonstrated increased metabolic activity in the right orbit, raising suspicion of disease relapse. Subsequent ophthalmologic assessment and additional imaging confirmed the presence of an orbital mass, which was surgically excised. Histopathological analysis verified a localized orbital recurrence of follicular lymphoma. The patient was subsequently treated with localized radiotherapy. Follow-up 18F-fluorodeoxyglucose positron emission tomography with computed tomography performed in 2023 demonstrated a complete metabolic response. **Conclusion.** The case highlights the important role of 18F-fluorodeoxyglucose positron emission tomography with computed tomography in detecting atypical and rare manifestations of follicular lymphoma. Integration of 18F-fluorodeoxyglucose positron emission tomography/computed tomography findings with ophthalmologic evaluation and histopathological confirmation is essential for accurate diagnosis and appropriate therapeutic decision-making.

**Key words:** Lymphoma, Follicular; Positron Emission Tomography Computed Tomography; Fluorodeoxyglucose F18; Recurrence; Orbital Neoplasms; Diagnosis; Radiotherapy

**Acknowledgement**
The study was supported by Grant No 451-03-137/2025-03/ 200110 Ministry of Science, Technological Development and Innovation.

**Sažetak**

**Uvod.** Intraorbitalna lokalizacija folikularnog limfoma je izuzetno retka, a postavljanje dijagnoze predstavlja izazov zbog širokog spektra mogućih oftalmoloških diferencijalnih dijagnoza. Prikazujemo slučaj pacijenta sa prethodno lečenim folikularnim limfomom, kod koga je pet godina nakon potpune remisije, detektovan relaps u desnoj orbiti putem 18F-fluorideoksiglukozne pozitronske emisione tomografije sa kompjuterizovanom tomografijom. **Prikaz slučaja**. Pacijent muškog pola i starosti 53 godine, kome je 2013. godine postavljena dijagnoza folikularnog limfoma, postigao je potpunu remisiju tokom 2017. godine, nakon sprovedene hemioterapije. Narednih pet godina bio je bez znakova relapsa osnovne bolesti. Tokom 2022. godine, pacijent je prijavio bol u desnom oku u trajanju od deset dana, dok su kliničkim pregledom ustanovljeni egzoftalmus i ptoza desnog kapka. Na 18F-fluorodeoksiglukoznoj pozitronskoj emisionoj tomografiji sa kompjuterizovanom tomografijom koja je sprovedena 2022. godine, prikazala se fokalna zona pojačanog nakupljanja fluorodeoksiglukoze u desnom oku, što je izazvalo sumnju na atipični relaps osnovne bolesti. Naknadna oftalmološka evaluacija ukazala je na intraorbitalni tumor, koji je hirurški uklonjen. Histopatološka analiza utvrdila je da se radi o orbitalnom relapsu folikularnog limfoma. Kod pacijenta je sprovedena radioterapija desnog oka. Kontrolna 18F-fluorodeoksiglukozna pozitronska emisiona tomografija sa kompjuterizovanom tomografijom iz 2023. godine pokazala je potpunu metaboličku regresiju prethodno opisane fokalne zone pojačane akumulacije radiofarmaka. **Zaključak.** Predstavljeni prikaz slučaja ukazuje da 18F-fluorodeoksiglukozna pozitronska emisiona tomografija sa kompjuterizovanom tomografijom ima važnu ulogu u otkrivanju atipičnih manifestacija folikularnog limfoma, dok je integracija nalaza 18F-fluorodeoksiglukozne pozitronske emisione tomografije sa oftalmološkom evaluacijom i patohistološkom analizom neophodna za postavljanje tačne dijagnoze i odabira optimalne terapije.

**Ključne reči**: folikularni limfom; PET/CT; FDG; relaps; tumori orbite; dijagnoza; radioterapija

✉ Corresponding author: Milica Kotur, E-mail: koturmilica99@gmail.com

***Abbreviations***

| | |
|---|---|
| FL | – follicular lymphoma |
| NHL | – non-Hodgkin lymphoma |
| FDG PET/CT | – Fluorodeoxyglucose positron emission tomography/Computed Tomography |
| PET/CT | – Positron Emission Tomography/Computed Tomography |

## Introduction

Follicular lymphoma (FL) is the most common indolent subtype of non-Hodgkin lymphoma (NHL) and typically presents with lymphadenopathy. Extranodal involvement in FL is uncommon and most frequently affects the gastrointestinal tract, skin, or central nervous system [1–5]. Intraorbital localization of FL relapse is exceedingly rare and represents a considerable diagnostic challenge, particularly in patients without prior orbital involvement [6]. This diagnostic complexity arises from a broad spectrum of differential diagnoses, including inflammatory conditions, primary intraorbital tumors, and metastatic lesions. Early recognition of such atypical presentations is therefore essential for timely intervention and appropriate therapeutic decision-making.

18F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) plays a central role in the management of lymphoma across different disease stages, including initial staging, assessment of suspected relapse, and evaluation of treatment response [7].

We report the case of a patient with previously treated FL who developed right orbital pain, exophthalmos, and eyelid ptosis five years after achieving complete remission. The relapse was ultimately diagnosed as intraorbital FL recurrence. The aim of this report is to highlight the diagnostic value of the FDG PET/CT in disease staging and treatment monitoring in patients with rare extranodal manifestations of FL.

## Case report

A 53-year-old man was diagnosed with FL in 2013 based on histopathological examination and was treated with systemic chemotherapy. At the time of diagnosis, FDG PET/CT demonstrated involvement of the submandibular, cervical, and mediastinal lymph nodes. Complete remission was achieved in 2017. Over the subsequent five years, the patient remained asymptomatic and underwent regular follow-up with FDG PET/CT examinations, without requiring additional treatment.

In 2022, five years after achieving disease remission, the patient presented for a routine follow-up FDG PET/CT examination. During medical history assessment, he reported a 10-day history of right eye pain. Clinical examination revealed right-sided exophthalmos and ptosis of the upper eyelid.

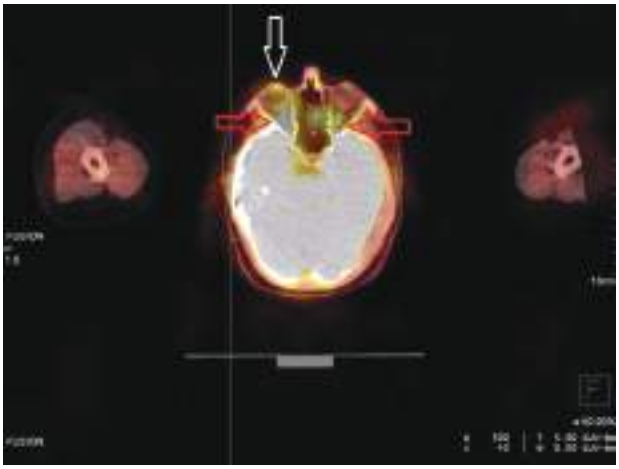

**Figure 1.** Fluorodeoxyglucose positron emission tomography/Computed Tomography before radiotherapy shows apparent focal FDG uptake within the right eye (white arrow) (SUVmax 5.1) – histopathologically confirmed as follicular lymphoma, while symmetric retrobulbar hypermetabolism can be seen bilaterally (red arrows) (SUVmax up to 8.1).

Whole-body FDG PET/CT imaging was performed using a 64-slice Biograph True64 PET/CT hybrid system (Siemens Medical Solutions USA Inc., Malvern, PA, USA), 90 minutes after intravenous administration of 269 MBq of 18F-FDG. The images revealed a focal area of increased FDG uptake in the right orbit. Given the non-specific nature of FDG accumulation, the findings raised suspicion for several possible etiologies, including relapse of FL, a primary orbital malignancy, or an inflammatory process **(Figure 1).** Additionally, symmetrical retrobulbar regions of increased glucose metabolism were observed bilaterally. Although these findings were most consistent with physiological uptake, pathological causes could not be entirely excluded **(Figure 1).** An ophthalmological consultation was therefore recommended.

Subsequent ophthalmological evaluation prompted additional radiological imaging, which demonstrated a tumorous mass within the right orbit. The report indicated no pathological changes involving the right eyeball itself. **Figure 2** outlines the chronological diagnostic steps leading to the final diagnosis.

Surgical exploration of the right orbit was performed via a superotemporal skin incision below the superior orbital rim. The lesion was completely excised, and the specimen was submitted for histopathological analysis. However, available radiological and surgical documentation did not allow precise determination of the lesion's exact anatomical localization within the orbital compartment.

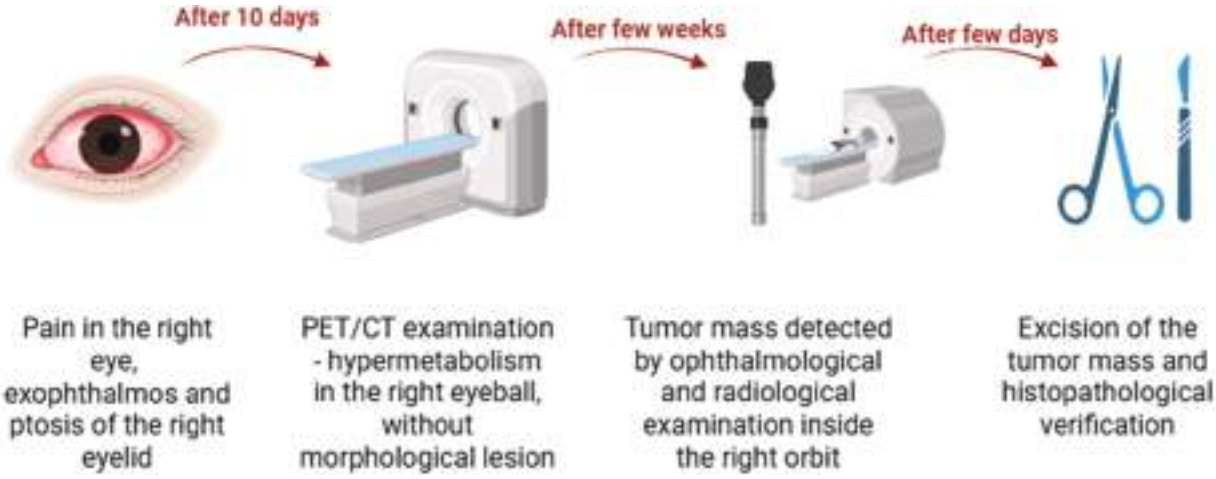


**Figure 2.** Timeline of diagnostics in right orbital follicular lymphoma relapse

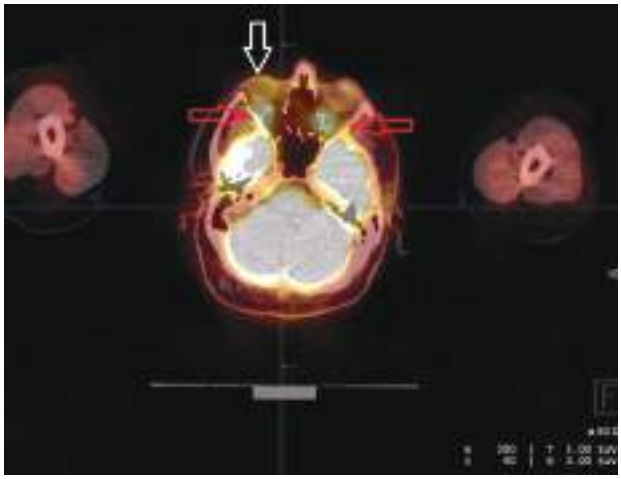

**Figure 3**. On post-radiotherapy Fluorodeoxyglucose positron emission tomography/Computed Tomography, the previously noted focal FDG uptake is no longer visible (white arrow), while symmetric retrobulbar FDG uptake, representing physiological uptake, is still observed (red arrows) (SUVmax up to 7.7)

Histopathological examination revealed a lymphoid neoplasm with a predominantly follicular growth pattern and infiltration of adjacent tissues. The tumor consisted mainly of centrocyte-like cells with admixed centroblasts. Immunohistochemical analysis demonstrated positivity for CD20, PAX5, CD79a, CD10, BCL2, and BCL6, and negativity for CD3, CD5, Cyclin D1, and MUM1. The Ki-67 proliferation index was approximately 20%, with focal increase up to 40%. These findings were consistent with grade 3A follicular lymphoma.

The patient subsequently underwent local radiotherapy, receiving a total of 25.5 Gy in 17 fractions. Four months after completion of radiotherapy, a follow-up FDG PET/CT examination was performed.

The follow-up imaging demonstrated complete metabolic regression of the disease, corresponding to a Deauville score of 2. This conclusion was based on the complete resolution of previously observed pathological FDG uptake in the right orbital region, indicating a complete local therapeutic response **(Figure 3)**. The symmetrical retrobulbar hypermetabolic areas remained unchanged compared to the prior examination, confirming their physiological nature (Figure 3). Key FDG PET/CT findings before and after radiotherapy are summarized in **Table 1**, illustrating complete metabolic response in the right orbit with no evidence of new pathological uptake elsewhere.

## Discussion

The present case illustrates an exceptionally rare relapse of follicular lymphoma (FL) involving the

**Table 1.** Comparative presentation of metabolic activity on initial and follow-up Fluorodeoxyglucose positron emission tomography/Computed Tomography

| Findings | Before RT FDG PET/CT | After RT FDG PET/CT |
|---|---|---|
| FDG uptake in the right eye | Pathological focal uptake | No pathological uptake |
| FDG uptake in retrobulbar region | Symmetric hypermetabolism | Symmetric hypermetabolism |
| FDG pathological uptake in other parts of the body | None | None |
| Clinical correlation | Relapse of follicular lymphoma confirmed by histopathology | Complete metabolic response |

RT – radiotherapy; FDG – 18F-Fluorodeoxyglucose; PET/CT – Positron Emission Tomography/Computed Tomography

right orbit following a prolonged disease-free interval and achievement of complete remission. Its clinical relevance lies in emphasizing the necessity of long-term surveillance, as FL may relapse even after several years of stable remission [8]. Importantly, relapse can occur despite an initially favorable therapeutic response and may involve anatomical sites not previously affected by the disease.

FDG PET/CT played a pivotal role in this case by detecting focally increased FDG uptake in the right ocular region, which prompted further diagnostic investigation. On the initial examination, the increased uptake appeared to be localized within the right eyeball and was interpreted as focal intraocular hypermetabolism. However, subsequent radiological assessment identified an intraorbital mass that was not clearly delineated on the FDG PET/CT images.

This apparent discrepancy can be explained by the spillover effect of metabolic activity from the adjacent intraorbital tumor, combined with reactive metabolic changes in displaced ocular structures and the inherent spatial resolution limitations of PET imaging. Consequently, FDG uptake originating from the intraorbital lesion may have been projected onto the globe, creating the false impression of intraocular involvement on PET/CT images [9,10]. Additionally, the retrobulbar mass detected by other imaging modalities may not have been sufficiently large at the time of the FDG PET/CT examination to be visualized on the low-dose, non-contrast CT component of the hybrid scan. This explanation is supported by the short duration of symptoms – only 10 days prior to imaging – suggesting that the orbital lesion was in an early stage of development.

It is well recognized that FDG PET/CT may demonstrate physiological FDG uptake in the ocular region, particularly within the extraocular muscles. Nevertheless, asymmetrical focal FDG accumulation in one eye relative to the contralateral side should raise suspicion for an underlying pathological process. FDG PET/CT is highly sensitive for the detection of extranodal lymphoma and frequently identifies disease sites that may be overlooked by other diagnostic modalities [11]. In the present case, the symmetrical retrobulbar FDG uptake observed bilaterally was deemed physiological, and it remained unchanged on follow-up imaging, whereas the pathological hypermetabolic focus in the right orbital region completely resolved after radiotherapy.

The differential diagnosis in this case was broad and included FL recurrence, primary intraocular malignancies such as uveal melanoma, idiopathic inflammatory orbital disease, and infectious processes [12]. Consequently, comprehensive ophthalmological evaluation and surgical excision of the lesion were required, enabling definitive histopathological confirmation of FL relapse. Although FDG PET/CT is an invaluable tool in the assessment of lymphoma, histopathological analysis remains the diagnostic gold standard, as imaging alone cannot reliably distinguish lymphoma from other intraocular pathologies.

Despite the inability of FDG PET/CT to initially visualize the orbital mass directly – likely due to spatial resolution constraints and early lesion size – the identification of abnormal hypermetabolism in the right ocular region during routine follow-up was crucial. This finding led to a timely referred for further diagnostic procedures, allowing prompt visualization, surgical excision, and initiation of appropriate therapy. Subsequent FDG PET/CT demonstrated complete metabolic response, underscoring the additional value of this modality in monitoring therapeutic efficacy.

## Conclusion

The case highlights several important clinical points: (1) Follicular lymphoma may relapse after a prolonged period of remission and may present in exceptionally rare extranodal locations; (2) Fluorodeoxyglucose positron emission tomography plays a crucial role in the detection of atypical extranodal manifestations of lymphoma; and (3) Accurate diagnosis and optimal treatment selection require integration of Fluorodeoxyglucose positron emission tomography findings with ophthalmological assessment and histopathological confirmation.

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# PARADOXICAL SINUS DECELERATION DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY – DIAGNOSTIC SIGNIFICANCE AND THERAPEUTIC APPROACH

# *PARADOKSALNA SINUSNA DECELERACIJA TOKOM DOBUTAMINSKOG STRES-EHOKARDIOGRAFSKOG TESTA – DIJAGNOSTIČKI ZNAČAJ I TERAPIJSKI PRISTUP*

**Borislav DOLAMIĆ[1], Ana ALADIN DOLAMIĆ[2], Anđelko HLADIŠ[1], Dragoslava ŽIVKOV ŠAPONJA[3] and Anastazija STOJŠIĆ MILOSAVLJEVIĆ[1,4]**

ORCID NUMBER
Borislav Dolamić – 0009-0006-1122-7181
Ana Aladin Dolamić – 0009-0004-3460-2082
Anđelko Hladiš – 0009-0006-5023-2960
Dragoslava Živkov Šaponja – 009-005-4216-9781
Anastazija Stojšić Milosavljević – 0000-0003-2092-4289

Military Hospital, Novi Sad[1]
Institute for Health Care of Children and Youth of Vojvodina, Novi Sad[2]
Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica[3]
University of Novi Sad, Faculty of Medicine Novi Sad[4]

Case report
*Prikaz slučaja*
UDK 616.12-07/-08
https://doi.org/10.2298/MPNS2512300D

**Abstract**

**Introduction.** Paradoxical sinus deceleration is an uncommon hemodynamic response observed during dobutamine stress echocardiography, characterized by a decrease in heart rate despite escalating doses of dobutamine, with or without a concomitant reduction in arterial blood pressure. Earlier studies associated this phenomenon with inferior myocardial ischemia, whereas more recent evidence suggests a potential autonomic mechanism mediated by activation of the Bezold–Jarisch reflex, particularly in the absence of left ventricular segmental wall motion abnormalities. The reported incidence of paradoxical sinus deceleration ranges from 5% to 10%, and its clinical significance appears to depend primarily on the presence of inducible ischemia. **Case Report.** A 53-year-old woman with arterial hypertension, dyslipidemia, and a positive family history of cardiovascular disease was evaluated for atypical anginal symptoms. At the maximal dose of dobutamine, asymptomatic paradoxical sinus deceleration accompanied by transient hypotension was observed. Electrocardiography revealed no ischemic changes or rhythm disturbances, and echocardiography demonstrated no left ventricular segmental wall motion abnormalities. The examination was therefore interpreted as negative for inducible myocardial ischemia. **Conclusion.** In the absence of echocardiographic evidence of ischemia, paradoxical sinus deceleration during dobutamine stress echocardiography does not represent an independent indication for invasive diagnostic procedures. The absence of left ventricular segmental wall motion abnormalities is pivotal in therapeutic decision-making, and conservative medical management with structured clinical follow-up constitutes a rational and safe approach.

**Key words:** Echocardiography, Stress; Dobutamine; Heart Rate; Arrhythmia, Sinus; Myocardial Ischemia; Electrocardiography; Hypotension; Cardiovascular Diseases; Reflex

**Sažetak**

**Uvod.** Paradoksalna sinusna deceleracija predstavlja retku hemodinamičku reakciju tokom dobutaminskog stres-ehokardiografskog testa, karakterisanu padom srčane frekvencije pri porastu doze dobutamina, sa sniženjem arterijskog krvnog pritiska ili bez njega. Raniji radovi dovodili su ovu pojavu u vezu sa inferiornom ishemijom miokarda, dok novija istraživanja ukazuju na mogući mehanizam autonomne regulacije u okviru Bezold–Jariševog refleksa, naročito u odsustvu poremećaja segmentne kinetike leve komore. Učestalost se procenjuje na 5–10%, a klinički značaj zavisi od prisustva inducibilne ishemije. **Prikaz slučaja.** Pacijentkinja starosti 53 godine sa arterijskom hipertenzijom, dislipidemijom i pozitivnom porodičnom anamnezom na kardiovaskularne bolesti ispitivana je zbog atipičnih anginoznih tegoba. Pri maksimalnoj dozi dobutamina registrovana je asimptomatska paradoksalna sinusna deceleracija sa prolaznom hipotenzijom, bez bola u grudima. Elektrokardiografski nisu evidentirani znaci ishemije niti poremećaji ritma, dok ehokardiografski nije utvrđen poremećaj segmentne kinetike leve komore. Nalaz je ocenjen kao negativan na inducibilnu ishemiju miokarda. **Zaključak.** U odsustvu ehokardiografskih znakova ishemije, paradoksalna sinusna deceleracija tokom dobutaminskog stres-ehokardiografskog testa ne predstavlja samostalnu indikaciju za invazivnu dijagnostiku. Odsustvo poremećaja segmentne kinetike leve komore ima presudan značaj u donošenju terapijske odluke, a medikamentno lečenje uz kliničko praćenje predstavlja racionalan i bezbedan pristup.

**Ključne reči:** stress ehokardiografija; dobutamine; srčana frekvencija; sinusna aritmija; miokardna ishemija; elektrokardiografija; hipotenzija; kardiovaskularna oboljenja; refleks

## Introduction

Dobutamine stress echocardiography (DSE) is a well-established non-invasive diagnostic modality for the detection of inducible myocardial ischemia, particularly in patients unable to perform exercise testing or in those with an intermediate or high pre-test probability of chronic coronary artery disease (CAD). Although dobutamine is primarily administered for its positive inotropic and chronotropic effects, paradoxical hemodynamic responses may occur during pharmacological stress testing. One such response is para-

✉ Corresponding author: Borislav Dolamić, E-mail: boradolamic@yahoo.com, anastazija.stojsic@mf.uns.ac.rs

***Abbreviations***

| | |
|---|---|
| DSE | – Dobutamine Stress Echocardiography |
| PSD | – Paradoxical Sinus Deceleration |
| RR interval | – interval between two R waves on electrocardiogram |
| D2 | – standard limb lead II |
| aVF | – augmented unipolar limb lead directed toward the inferior wall of the heart |
| CT | – computed tomography |

doxical sinus deceleration (PSD), defined as an unexpected decrease in heart rate during escalating doses of dobutamine, most commonly observed at peak pharmacological stress, with or without a concomitant reduction in arterial blood pressure. Available data indicate an incidence of 5-10% during DSE [1–3]. The underlying pathophysiological mechanism is most frequently attributed to activation of the Bezold–Jarisch reflex, which involves stimulation of mechanoreceptors and chemoreceptors located predominantly in the inferoposterior left ventricular wall. This reflex is mediated via enhanced vagal tone, resulting in bradycardia and hypotension [4]. While earlier studies considered PSD an indirect marker of ischemia, more recent investigations suggest that its association with hemodynamically significant CAD is heterogeneous and lacks sufficient specificity [1,3,5].

## Case Report

A fifty-three-year-old woman was referred for cardiological evaluation as part of routine follow-up for arterial hypertension. Her medical history included intermittent atypical chest discomfort without a clear relationship to physical exertion. The family history was positive for ischemic heart disease at a comparable age. Present cardiovascular risk factors included arterial hypertension, dyslipidemia, and active smoking. On physical examination, the patient was hemodynamically stable, with blood pressure 120/70 mmHg. Electrocardiography showed sinus rhythm at 63 beats per minute, normal intervals, and no signs of ischemia or arrhythmia. Resting transthoracic echocardiography demonstrated preserved left ventricular ejection fraction, absence of segmental wall motion abnormalities, and no evidence of diastolic dysfunction. Holter monitoring revealed sustained sinus rhythm, rare isolated supraventricular and ventricular premature beats, no RR pauses, no conduction disturbances, and no ischemic changes. Laboratory analysis indicated mild hypercholesterolemia. During DSE, dobutamine was administered up to a maximal dose of 40 μg/kg/min. At peak pharmacological stress, an asymptomatic decrease in heart rate from 134 to 100 beats per minute was observed, accompanied by a reduction in blood pressure from 140/90 mmHg to 100/60 mmHg. The patient did not report any anginal

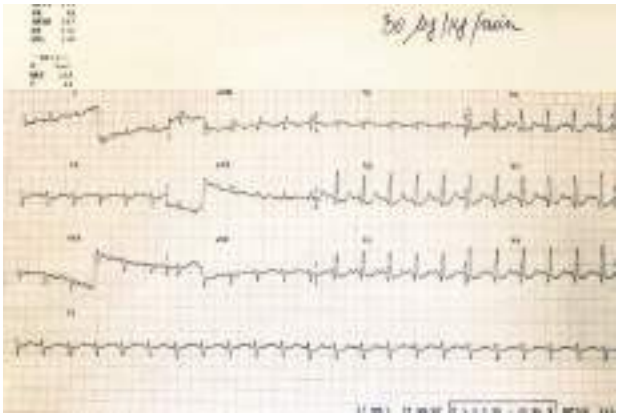

**Figure 1.** Electrocardiogram at dobutamine dose of 30 μg/kg/min

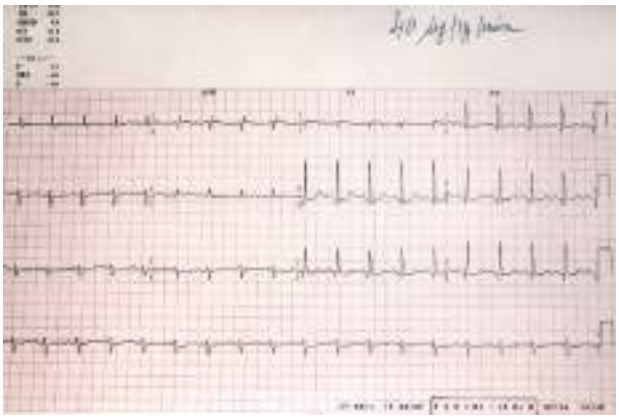

**Figure 2.** Electrocardiogram at dobutamine dose of 40 μg/kg/min

symptoms. Electrocardiographically, shallow biphasic T waves were noted in leads D2 and aVF at dobutamine doses of 30 and 40 μg/kg/min **(Figures 1 and 2).** However, echocardiographic assessment revealed no left ventricular segmental wall motion abnormalities during peak stress or recovery **(Figures 3 and 4).** Based on these findings, there was no evidence of re-

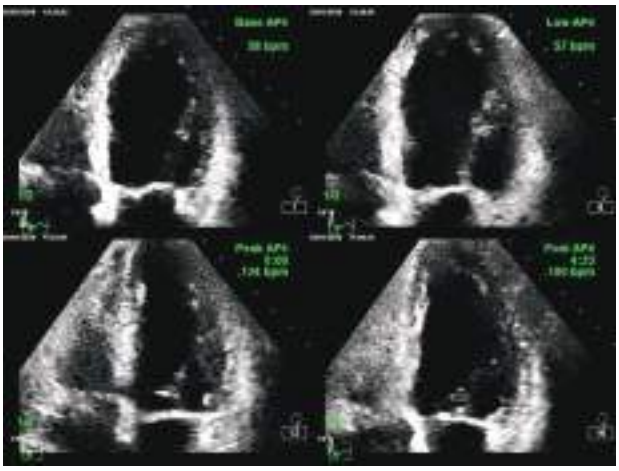

**Figure 3.** Diastolic phase during DSE assessment

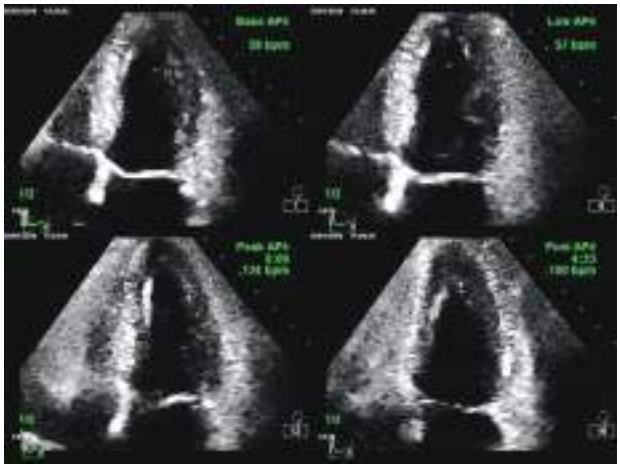

**Figure 4.** Systolic phase during DSE assessment

duced coronary reserve, and optimal medical therapy with continued clinical follow-up was recommended.

## Discussion

Paradoxical sinus deceleration (PSD) during dobutamine stress echocardiography (DSE) represents a complex and not yet fully elucidated phenomenon. Discrepancies between earlier and more recent studies may be explained by differences in study design, patient selection, and the availability of advanced non-invasive imaging modalities.

In the classic study by Attenhofer Jost et al. [3], which included patients referred for DSE due to suspected ischemic heart disease, coronary angiography was performed in most individuals exhibiting PSD. Significant CAD (>50% stenosis) was identified in approximately 57% of these patients, most frequently involving the right coronary artery. These findings supported the hypothesis that PSD was an indirect marker of inferior ischemia in the context of limited coronary reserve.

Conversely, a more recent case series by Sulo et al. [1] employed a more selective diagnostic strategy, including more frequent use of coronary computed tomography (CT) angiography and stricter criteria for invasive procedures. In that cohort, a substantial portion of patients with PSD had no hemodynamically significant CAD, and no increase in cardiovascular events was observed during follow-up among those managed conservatively. The authors concluded that PSD often reflects a functional autonomic response rather than a direct manifestation of myocardial ischemia. These divergent findings may also reflect differences in baseline cardiovascular risk. Earlier investigations predominantly included patients with higher pre-test probabilities of CAD, whereas contemporary cohorts often comprise individuals with atypical symptoms and low-to-intermediate risk profiles.

Current guidelines emphasize that the absence of stress-induced segmental wall motion abnormalities confers a high negative predictive value for hemodynamically significant CAD [5–8]. In this context, isolated electrocardiographic changes or hemodynamic responses – such as PSD and associated hypotension – lack sufficient diagnostic specificity when not accompanied by echocardiographic evidence of ischemia.

This interpretation is further supported by studies demonstrating an extremely low incidence of future cardiovascular events in patients with negative stress echocardiography findings [2,7,9,10]. Although PSD during DSE frequently occurs in the absence of segmental wall motion abnormalities and does not, in itself, indicate inducible ischemia, transthoracic echocardiography remains essential for comprehensive assessment of cardiac function and for ensuring procedural safety. As highlighted by Vulin et al., standard electrocardiographic parameters alone may be insufficient for precise diagnostic stratification, whereas echocardiographic assessment provides a more reliable basis for therapeutic decision-making [11]. The presented case is consistent with the contemporary interpretative framework of DSE, wherein the decision to defer coronary angiography is primarily guided by the absence of segmental wall motion abnormalities, stable clinical status, and supporting evidence from current literature.

## Conclusion

Paradoxical sinus deceleration during dobutamine stress echocardiography is a relatively uncommon but well-recognized hemodynamic response. In the absence of stress-induced segmental wall motion abnormalities, paradoxical sinus deceleration does not constitute an independent indication for coronary angiography. This case illustrated that a conservative pharmacological strategy combined with structured clinical follow-up is both justified and safe in appropriately selected patients.

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Rad je primljen 3. II 2026.
Recenziran 23. II 2026.
Prihvaćen za štampu 24. II 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:300-303.

# ONE SESSION, TWO TARGETS – COMBINED ENDOSCOPIC THIRD VENTRICULOSTOMY AND PINEAL CYST FENESTRATION –IN THE TREATMENT OF OBSTRUCTIVE HYDROCEPHALUS

# *JEDNA INTERVENCIJA, DVA CILJA – KOMBINOVANA ENDOSKOPSKA TREĆA VENTRIKULOSTOMIJA I FENESTRACIJA PINEALNE CISTE U LEČENJU OPSTRUKTIVNOG HIDROCEFALUSA*

**Dragana TEŠIĆ[1], Srđan STANKOVIĆ[1], Sara AZARIĆ[1], Snežana ZORIĆ[1], Veljko PANTELIĆ[1,2] and Jagoš GOLUBOVIĆ[1,2]**

ORCID NUMBER
Dragana Tešić – 0009-0008-9535-638X
Srđan Stanković – 0009-0002-7750-9051
Sara Azarić – 0009-0008-8773-5785
Snežana Zorić – 0009-0005-7229-7178
Veljko Pantelić – 0009-0008-1875-3592
Jagoš Golubović – 0000-0001-5524-246X

University of Novi Sad, Faculty of Medicine Novi Sad[1]
University Clinical Center of Vojvodina, Novi Sad
Clinic for Neurosurgery[2]

Case report
*Prikaz slučaja*
UDK 616.43-003:616.831-005]-07/-08
https://doi.org/10.2298/MPNS2512304T

**Abstract**
**Introduction.** Symptomatic pineal cysts are rare, and their optimal management remains controversial and not clearly defined. **Case Report.** We present a case of a 45-year-old female who presented with several weeks of headache and acute-onset vertigo beginning the night prior to admission. Her medical history included an asymptomatic pineal cyst incidentally identified on magnetic resonance imaging two years earlier. Current imaging demonstrated marked enlargement of the pineal cyst with compression of the Sylvian aqueduct, resulting in obstructive hydrocephalus. The patient underwent a single-session combined endoscopic procedure with neuronavigation guidance. An endoscopic third ventriculostomy was first performed via a right frontal burr hole (Kocher's point) to restore cerebrospinal fluid circulation. Through a second frontal burr hole, the pineal cyst wall was fenestrated and a biopsy was obtained. Both procedures were performed with the patient in the supine position and neutral head alignment. No intraoperative or postoperative complications were observed. Postoperative computed tomography confirmed ventriculostomy patency and reduction in ventricular size. At three-month follow-up, the patient remained asymptomatic. **Conclusion.** A combined minimally invasive endoscopic approach can effectively addressed both obstructive hydrocephalus and symptomatic pineal cyst in a single surgical session.
**Key words:** Hydrocephalus; Third Ventricle; Ventriculostomy; Pineal Gland; Cyst; Endoscopy; Minimally Invasive Surgical Procedures

**Sažetak**
**Uvod.** Simptomatske pinealne ciste su retke, a njihov tretman je i dalje kontroverzan i nejasno definisan. **Prikaz slučaja.** Prikazujemo slučaj 45-godišnje pacijentkinje koja se javila zbog glavobolje koja traje nekoliko nedelja i vrtoglavice koja je počela veče pre prijema. U medicinskoj istoriji postojala je asimptomatska cistična lezija pinealne žlezde, slučajno otkrivena na pregledu magnetnom rezonancom sprovedenom dve godine ranije. Magnetno-rezonantni imidžing je pokazao značajno uvećanje pinealne ciste, koja komprimuje moždani akvedukt dovodeći do opstruktivnog hidrocefalusa. Pacijentkinja je podvrgnuta kombinovanoj endoskopskoj proceduri u jednoj sesiji, uz upotrebu neuronavigacije. Najpre je urađena endoskopska treća ventrikulostomija kroz desni frontalni trepanski otvor (Koherova tačka) radi uspostavljanja protoka cerebrospinalne tečnosti. Kroz drugi, odvojeni frontalni trepanski otvor, izvršena je fenestracija zida pinealne ciste i uzet je uzorak tkiva za biopsiju. Oba zahvata urađena su u položaju na leđima, sa glavom u neutralnom položaju. Procedura je prošla bez intraoperativnih i postoperativnih komplikacija. Postoperativni nalaz kompjuterizovane tomografije je potvrdio prohodnost ventrikulostomije i redukciju veličine komora i ciste. Na kontrolnom pregledu sprovedenom nakon tri meseca pacijentkinja je bila bez simptoma. **Zaključak.** Ovakav kombinovani pristup omogućio je efikasno rešavanje i hidrocefalusa i same pinealne ciste, sprovedeno kroz jednu minimalno invazivnu proceduru.
**Ključne reči:** hidrocefalus; treći ventriculus; ventrikulostomija; pinealna žlezda; cista; endoskopija; minimalno invazivne hirurške procedure

## Introduction

Pineal cysts (PCs) are benign, non-neoplastic lesions arising from the pineal gland, typically located within the quadrigeminal cistern, with the anterior wall often protruding into the third ventricle [1]. They are predominantly asymptomatic and frequently identified as incidental findings on brain imaging, with a reported prevalence ranging from 1.3% to 4.5% in imaging studies and in up to 40% of autopsy series [2]. However, large pineal cysts may compress the quadrigeminal plate and obstruct the cerebral aqueduct, resulting in obstructive hydrocephalus and increased intracranial pressure [3]. In such cases, patients may

✉ Corresponding author: Dragana Tešić, E-mail: 911097d25@mf.uns.ac.rs, jagos.golubovic@mf.uns.ac.rs

***Abbreviations***

ETV – endoscopic third ventriculostomy
MRI – magnetic resonance imaging
CT – computed tomography
CSF – cerebrospinal fluid

develop headaches, seizures, or persistent neurological deficits, including ocular movement abnormalities.

Management strategies for pineal cysts depend on clinical presentation and symptomatology. Asymptomatic lesions are typically managed conservatively with interval magnetic resonance imaging (MRI) surveillance [4]. Surgical treatment options for symptomatic pineal cysts associated with hydrocephalus include ventriculoperitoneal shunting or endoscopic third ventriculostomy (ETV) for cerebrospinal (CSF) diversion, microsurgical cyst resection, endoscopic cyst fenestration, or combined endoscopic approaches [5].

In this report, we present a case of obstructive hydrocephalus caused by a pineal cyst successfully treated using a combined ETV and cyst fenestration performed during a single surgical session.

## Case Report

A 45-year-old women presented with several weeks of headaches followed by acute onset vertigo beginning the night prior to admission. Her medical history included an asymptomatic pineal cystic lesion incidentally identified on MRI two years earlier during evaluation for elevated oxytocin levels.

Neurological examination revealed bilateral papilledema, while the remainder of the examination was unremarkable. Brain MRI demonstrated a well-defined 24-mm cystic lesion with peripheral calcifications localized in the pineal region, compressing the cerebral aqueduct and resulting in marked dilation of the lateral and third ventricles, consistent with obstructive hydrocephalus secondary to a pineal cyst **(Figure 1A and B).** Based on clinical presentation, neurological findings, as imaging results, delayed-urgent neurosurgical intervention was indicated.

The surgical procedure consisted of two sequential steps:

1. Endoscopic Third Ventriculostomy (ETV): A right frontal burr hole was created at Kocher's point, and endoscopic fenestration of the floor of the third ventricle was performed to establish a CSF bypass.

2. Cystotomy and biopsy: A second frontal burr hole was created to allow endoscopic access to the pineal cyst, enabling fenestration of the cyst wall and tissue biopsy.

The patient was positioned supine with the head secured in a neutral alignment. Neuronavigation was utilized for trajectory planning and intraoperative guidance. A right frontal burr hole was made, and the right lateral ventricle was accessed via Kocher's point. A rigid endoscope was advanced along the planned trajectory, and the foramen of Monro was identified, permitting entry into the third ventricle. Using a monopolar instrument, fenestration of the third ventricular floor was performed, followed by enlargement with a balloon catheter to complete the ventriculostomy. CSF flow into the prepontine cistern was confirmed.

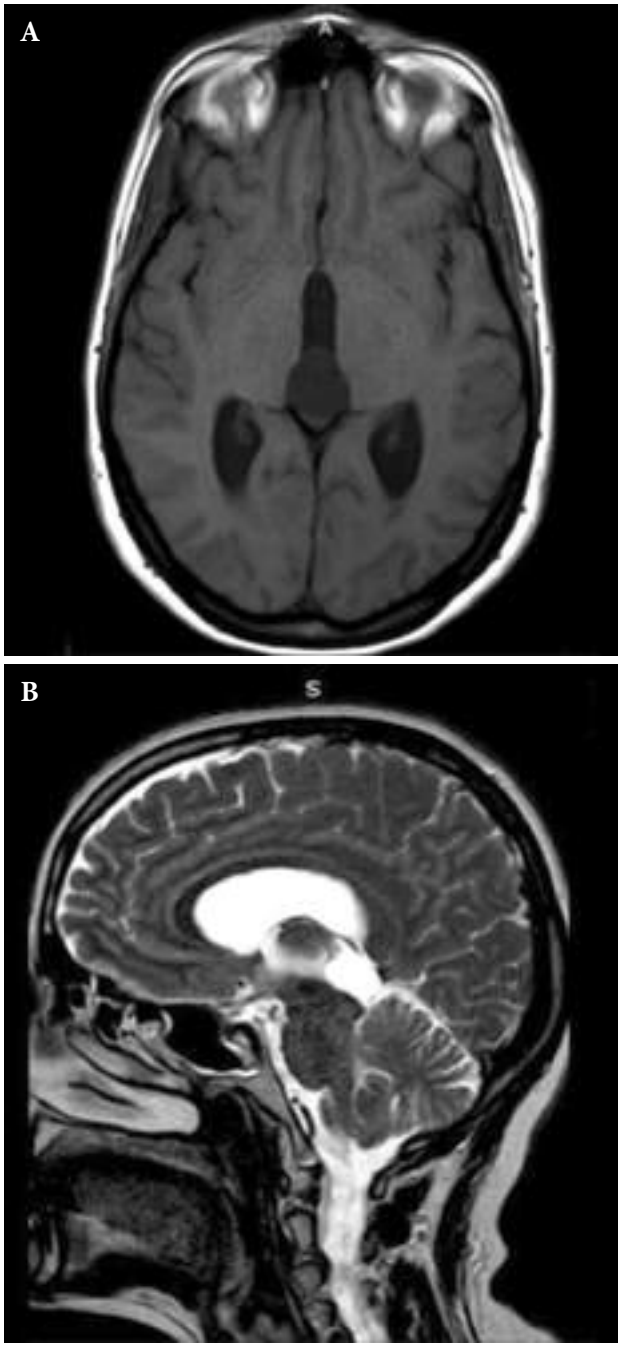


**Figure 1A and B.** Preoperative MRI images (A: axial T1-weighted; B: sagittal T2-weighted) demonstrating a cystic mass lesion measuring 24 mm in diameter in the pineal region, causing obliteration of the Sylvian aqueduct.

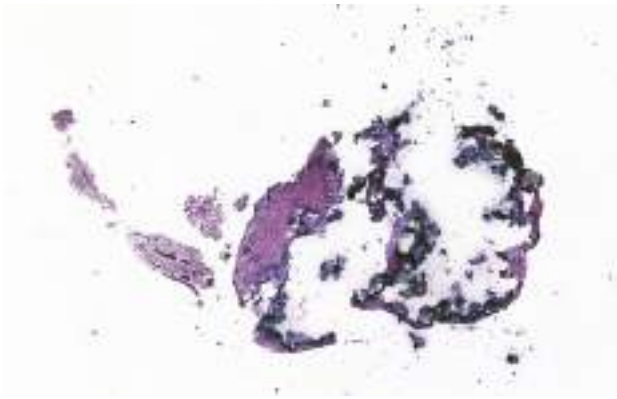

**Figure 2**. Histopathological appearance of a calcified pineal cyst (H&E staining). Fragments of a fibrotically thickened cyst wall with coarse lamellar and granular calcifications are present. No evidence of neoplastic proliferation is observed.

A second frontal burr hole was subsequently created anterior to the first. The frontal horn of the lateral ventricle was accessed according to navigation guidance, and the endoscope was reintroduced through the foramen of Monro into the third ventricle. A cystic lesion was identified posteriorly in the region of the Sylvian aqueduct. The cyst wall was fenestrated, establishing wide communication with the ventricular system, and a tissue sample was obtained for histopathological analysis.

After achieving adequate hemostasis, the wound was closed in anatomical layers. The total operative time for both procedures was 60 minutes (skin-to-skin).

The postoperative curse was uneventful. CT performed on the first postoperative day confirmed ventriculostomy patency, reduction in ventricular size, and regression of the cystic lesion. The patient was discharged on postoperative day four in good clinical condition.

Histopathological examination confirmed a simple pineal cyst without evidence of neoplastic changes **(Figure 2).** Follow-up MRI at three months demonstrated decreased ventricular dilation and reduction in cyst size **(Figure 3A and B).** The patient remained asymptomatic at follow-up.

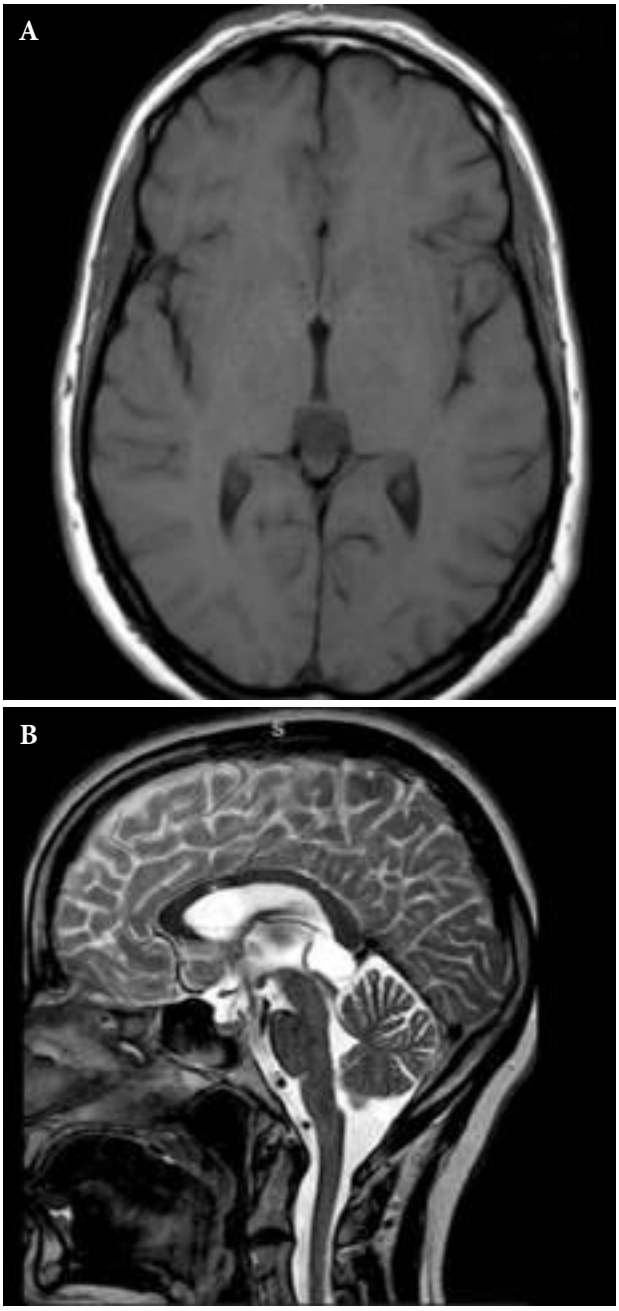


**Figure 3A and B.** MRI images obtained at 3-month follow-up (A: axial T1-weighted; B: sagittal T2-weighted) demonstrating postoperative changes, including reduced ventricular dilation and decreased size of the cystic lesion.

**Discussion**

Symptomatic pineal cysts are relatively uncommon but may result in life-threatening obstructive hydrocephalus due to compression of the cerebral aqueduct. When significant symptoms or radiological evidence of CSF pathway obstruction are present, surgical intervention is indicated [6]. Several treatment strategies have been described in the literature:

– **Ventriculoperitoneal shunting or endoscopic third ventriculostomy (ETV) alone**: These approaches provide CSF diversion but do not directly address the underlying cystic lesion. Consequently, the cyst may continue to enlarge or cause recurrent obstruction over time [7].

– **Microsurgical pinealectomy**: Open surgical removal of the cyst, typically via a supracerebellar infratentorial approach, may offer definitive treatment but is associated with greater surgical invasiveness and a higher risk of complications [8].

– **Endoscopic cyst fenestration alone**: This minimally invasive strategy enables direct decompression of the cyst into the CSF spaces; however, persistent or re-

current hydrocephalus may occur if aqueductal obstruction is not adequately resolved [3,9].

– **Combined ETV and cyst fenestration**: This approach simultaneously addresses both CSF flow obstruction and cyst compression by establishing an alternative CSF pathway while decompressing the lesion, potentially providing a more definitive and durable solution [3].

The combined endoscopic strategy used in the present case offers several advantages. It avoids the morbidity associated with open microsurgical approaches and eliminates the need for permanent shunt placement. ETV restores CSF circulation by creating an alternative pathway, while cyst fenestration directly decompresses the pineal lesion and allows tissue sampling for histological confirmation. Furthermore, neuronavigation enhances procedural safety by enabling accurate trajectory planning to deep-seated anatomical targets. In our patient, this approach resulted in immediate symptom relief without intraoperative or perioperative complications [4,10].

Although some reports describe symptom resolution following cyst fenestration alone, there remains a risk of recurrent aqueductal obstruction if the fenestration narrows or closes over time. Incorporating ETV into the procedure provides an additional safeguard for CSF circulation, potentially reducing the likelihood of recurrence [1,3]. To our knowledge, performing both procedures during a single operative session remains relatively infrequently reported. The sustained symptom-free status at three-month follow-up in our patient suggests that this combined approach may offer durable clinical benefits.

Potential risks associated with this dual procedure include bleeding or injury to adjacent critical structures, such as the internal cerebral veins [11]. However, meticulous preoperative planning and the use of intraoperative neuronavigation can substantially mitigate these risks [2,10]. The favorable outcome observed in this case supports the feasibility, safety, and effectiveness of single-session combined endoscopic ETV and cyst fenestration in appropriately selected patients.

## Conclusion

We present a case of obstructive hydrocephalus caused by a pineal cyst successfully treated using a minimally invasive combined approach consisting of endoscopic third ventriculostomy and cyst fenestration performed during a single surgical session. This strategy effectively resolved hydrocephalus, decompressed the cyst, and avoided the need for open surgery. The excellent clinical outcome and sustained symptom resolution at three-month follow up suggest that this combined endoscopic technique represents a safe and effective therapeutic option. Based on current literature and our experience, this minimally invasive approach may provide immediate symptom relief and a potentially definitive solution for elected patients with symptomatic pineal cysts.

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Rad je primljen 9. XII 2026.
Recenziran 27. I 2026.
Prihvaćen za štampu 27. I 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:304-307.

# CUSTOMIZED 3D-PRINTED BONE RESECTION GUIDE AND PMMA CRANIOPLASTY MOLD IN OSTEOLYTIC LESIONS – A CASE REPORT

# *PEROSNALIZOVANI TRODIMENZIONALLNI ŠTAMPANI VODIČ ZA RESEKCIJU KOSTI I KALUP ZA PMMA KRANIOPLASTIKU KOD OSTEOLITIČKIH LEZIJA – PRIKAZ SLUČAJA*

**Dušan RODIĆ[1,2], Marko DESPOTOVIĆ[1,2], Veljko PANTELIĆ[1], Jovana RODIĆ[3], Snežana ZORIĆ[4] and Jagoš GOLUBOVIĆ[1,2]**

ORCID NUMBER
Dušan Rodić – 0009-0007-2911-6217
Marko Despotović – 0009-0005-6917-5233
Veljko Pantelić – 0009-0008-1875-3592
Jovana Rodić – 0009-0006-0669-771X
Snežana Zorić – 0009-0005-7229-7178
Jagoš Golubović – 0000-0001-5524-246X

University Clinical Center of Vojvodina, Clinic for Neurosurgery, Novi Sad[1]
University of Novi Sad, Faculty of Medicine Novi Sad, Department for Surgery[2]
University Clinical Center of Vojvodina, Clinic for Gynecology and Obstetrics, Novi Sad[3]
University of Novi Sad, Faculty of Medicine Novi Sad[4]

Case report
*Prikaz slučaja*
UDK 616.714-089.843:004.8
https://doi.org/10.2298/MPNS2512308R

**Abstract**

**Introduction.** Osteolytic skull lesions pose significant surgical challenges because of their destructive nature and potential involvement of adjacent soft tissues. Complete resection of the affected bone is essential to reduce the risk of recurrence and ensure cranial stability; however this frequently results in large defects that require precise and immediate reconstruction. Advances in three-dimensional printing have enabled patient-specific surgical planning and the creation of customized tools and implants, thereby improving surgical accuracy, operative efficiency, and cosmetic outcomes. **Case Report.** We present a case of a patient with an osteolytic skull lesion treated using a customized three-dimensional-printed bone resection guide and a polylactic acid mold for intraoperative polymethyl methacrylate cranioplasty. Preoperative computed tomography and magnetic resonance imaging data were used to generate a virtual three-dimensional model, allowing accurate definition of resection margins and precise implant design. This approach enabled controlled lesion excision and immediate reconstruction using a well-fitting polymethyl methacrylate implant. Postoperative imaging confirmed complete lesion resection and optimal implant positioning, with excellent cosmetic and functional outcomes observed at one-year follow-up. **Discussion.** The integration of three-dimensional printing into cranial reconstructive surgery enhances surgical precision, reduces operative time, and offers a cost-effective method for individualized reconstruction. This case highlights the practical applicability of three-dimensional-printed surgical guides and molds in managing complex osteolytic skull lesions. **Conclusion**. The use of three-dimensional-printed resection guides combined with intraoperative polymethyl methacrylate molding enables accurate bone resection and immediate cranial reconstruction, achieving high precision, reproducibility, and favorable clinical outcomes.

**Key words:** 3D printing; osteolytic skull lesion; cranioplasty; Bone resection; PMMA; personalized surgery

**Sažetak**

**Uvod.** Osteolitičke lezije lobanje predstavljaju značajan hirurški izazov zbog svog destruktivnog karaktera i potencijalnog zahvatanja i kosti i okolnih mekih tkiva. Postizanje potpune resekcije zahvaćene kosti od suštinskog je značaja za smanjenje rizika od recidiva i obezbeđivanje strukturne stabilnosti, ali takav pristup često dovodi do velikih kranijalnih defekata koji zahtevaju preciznu i trenutnu rekonstrukciju. Napredak u tehnologiji trodimenzionalne štampe omogućio je individualno planiranje operacije i izradu implantata, čime su poboljšani preciznost, efikasnost operativnog zahvata i estetski ishodi. **Prikaz slučaja.** Prikazujemo slučaj bolesnice sa osteolitičkom lezijom lobanje koja je lečena primenom prilagođenog trodimenzionalno štampanog vodiča za resekciju kosti i kalupa od polilaktične kiseline za intraoperativnu kranioplastiku polimetilmetakrilatom. Preoperativni podaci dobijeni kompjuterizovanom tomografijom i magnetnom rezonacom iskorišćeni su za izradu virtuelnog trodimenzionalnog modela, koji je omogućio precizno određivanje margina resekcije i dizajn implantata. Ovaj pristup omogućio je precizno uklanjanje lezije i trenutnu rekonstrukciju sa dobro prilagođenim polimetilmetakrilatnim implantatom. Postoperativno snimanje potvrdilo je potpunu resekciju i adekvatno pozicioniranje implantata, uz odlične estetske i funkcionalne rezultate tokom jednogodišnjeg praćenja. **Diskusija.** Integracija trodimenzionalne štampe u kranijalnu rekonstruktivnu hirurgiju donosi veću tačnost, kraće trajanje operacije i ekonomičnu prilagodljivost. Ovaj slučaj naglašava praktičnu i inovativnu vrednost trodimenzionalne tehnologije u lečenju osteolitičkih lezija lobanje i optimizaciji rezultata kranijalne rekonstrukcije. **Zaključak**. Primena trodimenzionalno štampanih vodiča za resekciju u kombinaciji sa intraoperativnim oblikovanjem polimetilmetakrilata omogućava precizno uklanjanje lezije i neposrednu rekonstrukciju kranijuma sa zadovoljavajućim funkcionalnim i estetskim ishodima.

**Ključne reči:** 3D štampa; Osteolitička lezija lobanje; Kranioplastika; Resekcija kosti; PMMA; Personalizovana hirurgija

## Introduction

Osteolytic skull lesions comprise a heterogeneous group of pathological entities characterized by focal destruction of calvarial bone, often involving both cortical and cancellous layers. These lesions may result from primary bone tumors, metastatic disease, hematologic malignancies, infectious processes, or

✉ Corresponding author: Dušan Rodić, E-mail: dusan.rodic@mf.uns.ac.rs

***Abbreviations***

PMMA – polymethyl methacrylate
3D – three-dimensional
PLA – polylactic acid
CT – computed tomography
MRI – magnetic resonance imaging
PEEK – polyetheretherketone/polyether ether ketone
CAD – computer-aided design

inflammatory disorders [1,2]. Clinical presentation ranges from incidental asymptomatic findings to painful, palpable masses or neurological symptoms caused by intracranial extension. Regardless of etiology, osteolytic skull lesions pose sustainable surgical challenges owing to their often ill-defined margins, potential invasion of adjacent dura or soft tissues, and the cosmetic and functional consequences of bone resection [3,4]. Complete excision of the affected bone is essential to prevent recurrence or progressive osteolysis, however, such resections frequently result in large cranial defects that necessitate immediate and accurate reconstruction. Conventional reconstruction approaches – including autologous bone grafts, intraoperatively hand-molded polymethyl methacrylate (PMMA), and prefabricated alloplastic implants – are associated with several limitations, such as suboptimal anatomical fit, prolonged operative time, and variable cosmetic outcomes [5]. The integration of three-dimensional (3D) printing technology into cranial reconstructive surgery has significantly advanced both preoperative planning and intraoperative precision. Using high-resolution CT imaging, computer-aided design (CAD), and additive manufacturing, patient-specific surgical guides and reconstruction tools can now be fabricated with millimetric accuracy [6–8]. Customized bone resection guides enable precise delineation of resection margins while minimizing unnecessary bone loss, while intraoperative molds facilitate rapid fabrication of anatomically accurate PMMA implants. Together, these innovations improve surgical accuracy, reduce operative time, and enhance functional and aesthetic outcomes [8,9]. The availability of biocompatible printable materials such as polylactic acid (PLA) and polyetheretherketone (PEEK) has further expanded the scope of safe intraoperative customization [9,10]. This multidisciplinary strategy – combining neurosurgery, biomedical engineering, and materials science – represents a major advancement in patient-specific cranial reconstruction. In this report, we describe a case of an osteolytic skull lesion treated using a customized 3D-printed bone resection guide and an intraoperative PLA mold for PMMA cranioplasty, highlighting the precision and efficiency of this technique.

## Case Report

*Patient Information*

A 55-year-old female presented with headache and a palpable skull mass over the right frontoparietal region. Neurological examination revealed no focal deficits, although mild scalp tenderness was noted over the lesion. Imaging studies, including CT (Figure 1) and contrast-enhanced MRI, demonstrated a hyperostotic lesion in the right frontoparietal region with an associated soft-tissue component.

*Surgical Planning and 3D Printing Process*

Given the extent of bone involvement, a multidisciplinary approach was adopted, integrating neurosurgical, radiological, and biomedical engineering expertise. High-resolution CT and MRI datasets were

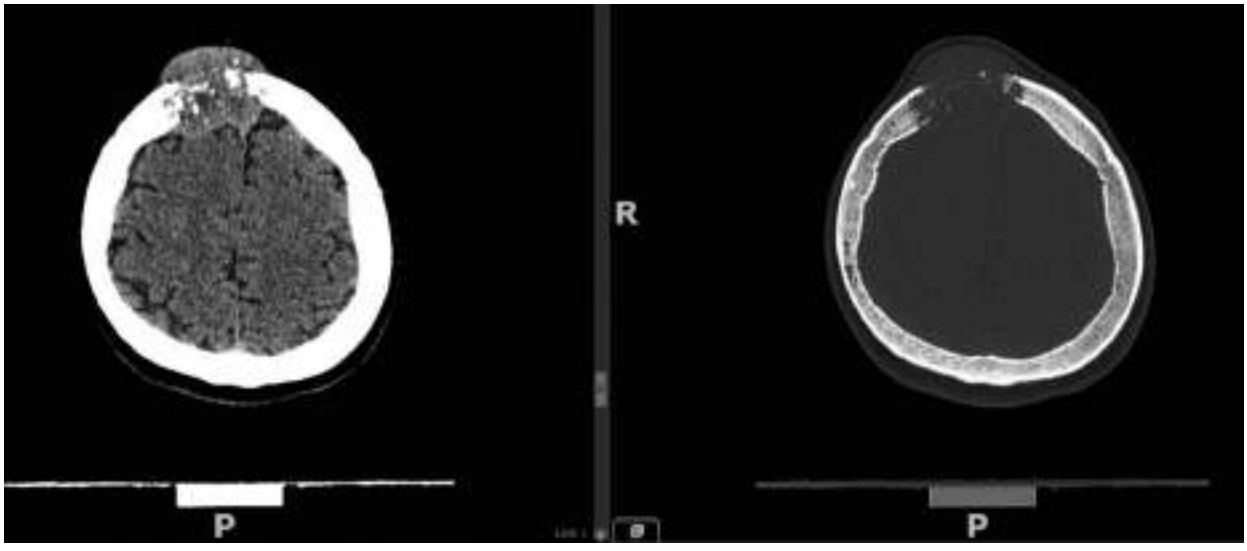


**Figure 1.** Preoperative endocranial CT – *osteolytic lesion*

processed using Fusion 360 CAD software to generate an accurate 3D model of the skull, lesion, and surrounding anatomical structures. This model enabled virtual surgical planning, including precise definition of resection margins while preserving critical neurovascular structures.

A patient-specific 3D-printed bone resection guide was designed to conform exactly to the cranial surface, ensuring accurate and reproducible bone removal. In addition, a PLA mold was created for intraoperative fabrication of a customized PMMA implant. Both the cutting guide and the mold were manufactured using polylactic acid and sterilized with ethylene oxide prior to surgery.

*Surgical Procedure*

A standard curved skin incision was performed to expose the hyperostotic bone. The PLA resection guide was positioned and secured, allowing for precise bone removal along the preplanned surgical margins. Guided resection facilitated complete excision of the involved bone, followed by microsurgical tumor removal while maintaining anatomical accuracy. After resection, the sterilized PLA mold was used intraoperatively to form a PMMA implant, which was contoured and polished to match the surrounding cranial anatomy. Fixation was achieved using stainless steel wires, providing stable reconstruction.

*Postoperative Outcome*

The postoperative course was uneventful. Follow-up CT imaging **(Figure 2)** confirmed complete lesion resection and accurate positioning of the PMMA implant. At one-year follow-up, the patient reported excellent cosmetic satisfaction and functional outcome, with no evidence of complications or recurrence.

**Discussion**

The application of 3D printing in cranial reconstructive surgery has substantially improved the management of osteolytic skull lesions. Traditional techniques based on intraoperative estimation and manual implant shaping are often associated with prolonged operative times and imprecise reconstruction, particularly in large or irregular cranial defects [6,7]. In contrast, patient-specific 3D-printed resection guides and molds enable highly accurate surgical planning and reconstruction that closely replicates native cranial anatomy. Preoperative 3D modeling allows precise visualization of lesion extent, facilitating controlled bone removal while protecting adjacent neurovascular structures [7]. In cases of metastatic or locally aggressive osteolytic disease, this approach improves oncological clearance by minimizing residual pathological bone [3]. Simultaneously, 3D-assisted reconstruction provides superior aesthetic results – an especially important consideration for anterior or frontotemporal defects, where cosmetic outcomes significantly influence postoperative quality of life [8,9].

The use of customized PLA molds for intraoperative PMMA cranioplasty eliminates labor-intensive manual shaping, reducing operative time and potential human error. PMMA remains a reliable and cost-effective cranioplasty material, offering excellent mechanical strength, contourability, and long-term biocompatibility [8]. The addition of 3D-printed molds further enhances implant precision, ensuring seamless integration with adjacent bone and reducing postoperative asymmetry [9]. Sterilization and biocompatibility remain important considerations.

Although PLA is unsuitable for permanent implantation, its application as a temporary intraoperative

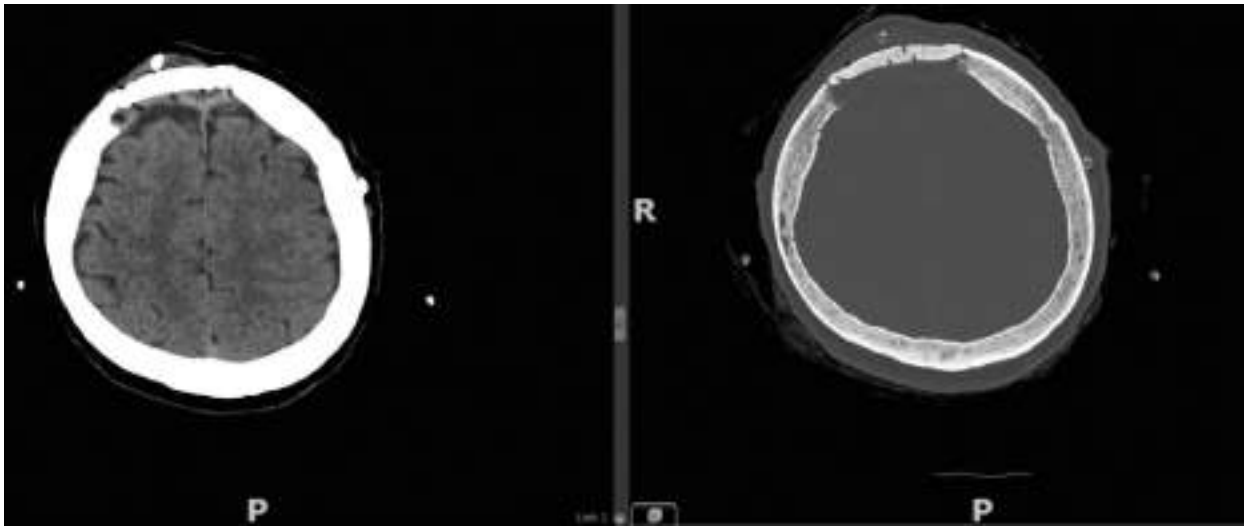


**Figure 2.** Postoperative endocranial CT – *PMMA implant*

guide or mold is safe when appropriately sterilized, most commonly using ethylene oxide [10]. Emerging printable biopolymers, including PEEK and composite resins with antibacterial coatings, may further improve long-term safety, sterility, and durability [9,10].

From an economic standpoint, in-house 3D printing represents a cost-effective alternative to commercially prefabricated implants, particularly in resource-limited healthcare settings [8]. The increasing availability of open-source software and affordable 3D printers has facilitated broader access to patient-specific cranial reconstruction, allowing neurosurgical teams to produce accurate surgical aids locally [9]. Nevertheless, successful implementation requires technical expertise in image segmentation, CAD modeling, and additive manufacturing [6]. Close collaboration among neurosurgeons, radiologists, and biomedical engineers is essential to ensure optimal outcomes. Establishing standardized protocols and training programs can promote wider adoption and consistency across institutions [10,11]. Future studies should focus on long-term outcomes of 3D-assisted reconstruction in osteolytic skull lesions, including implant stability, recurrence rates and patient satisfaction. Comparative analysis between conventional and 3D-guided cranioplasty techniques are also needed to further define clinical and cost-effectiveness [9–11]. As digital planning platforms continue to evolve, the integration of artificial intelligence for automated image segmentation and implant modeling may further streamline this process, enhancing both precision and accessibility. The combined use of 3D-printed resection guides and intraoperative PMMA molding represents a transformative advancement in the management of osteolytic skull lesions. This approach improves surgical accuracy, reduces operative time, and achieves superior cosmetic and structural outcomes. With ongoing developments in biocompatible materials and digital design technologies, patient-specific 3D printing is poised to become a cornerstone of contemporary cranial reconstructive surgery.

## Conclusion

Three-dimensional printed bone resection guides combined with intraoperative polymethyl methacrylate molding enable precise lesion resection and immediate reconstruction in patients with extensive osteolytic skull lesions. This approach enhances surgical accuracy, improves workflow efficiency, and yields favorable functional and cosmetic outcomes. Further prospective studies are warranted to assess long-term durability and to define the role of this technique in standard neurosurgical practice.

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Rad je primljen 18. XI 2025.
Recenziran 2. II 2026.
Prihvaćen za štampu 2. II 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:308-311.

# FROM COMA TO RECOVERY – A RARE CASE OF RUPTURED PONTINE CAVERNOMA IN A YOUNG PATIENT

# *OD KOME DO OPORAVKA – REDAK SLUČAJ RUPTURE KAVERNOMA PONSA KOD MLADE PACIJENTKINJE*

**Sara AZARIĆ[1], Dragana TEŠIĆ[1], Srđan STANKOVIĆ[1], Snežana ZORIĆ[1], Milica GLEĐA[2] and Jagoš GOLUBOVIĆ[1,2]**

ORCID NUMBER
Sara Azarić – 0009-0008-8773-5785
Dragana Tešić – 0009-0008-9535-638X
Srđan Stanković – 0009-0002-7750-9051
Snežana Zorić – 0009-0005-7229-7178
Milica Gleđa – 0009-0000-2100-4316
Jagoš Golubović – 0000-0001-5524-246X

University of Novi Sad, Faculty of Medicine Novi Sad[1]
University Clinical Center of Vojvodina, Novi Sad
Department of Neurosurgery[2]

Case report
*Prikaz slučaja*
UDK 616.83-005-06:616.8-08
https://doi.org/10.2298/MPNS2512312A

**Abstract**

**Introduction.** Cavernous hemangiomas are benign vascular malformations with an estimated prevalence of 0.4–0.8%. Pontine cavernomas account for approximately 14–30% of intracranial cavernous malformations and represent a significant therapeutic challenge due to the high density of critical neural pathways within the brainstem. Although technically demanding, surgical treatment may be lifesaving in carefully selected cases. **Case Report**. A 23-year-old woman with multiple supratentorial cavernomas was initially managed conservatively due to mild clinical symptoms. Nine months later, she was found unresponsive following sudden onset of headache and vomiting. On admission, she was in deep coma and required immediate endotracheal intubation. Computed tomography revealed a large pontine hemorrhage with obstructive hydrocephalus, and magnetic resonance imaging confirmed a markedly enlarged cavernoma with acute bleeding. Given her critical neurological condition, emergent surgery was performed to evacuate the hematoma, resect the cavernoma, and relieve brainstem compression. With intensive postoperative care and five months of structured neurorehabilitation, the patient demonstrated gradual neurological improvement, including recovery of the swallowing reflex, initiation of speech, and significant motor recovery. At one-year follow-up, she achieved full cognitive recovery, normal communication abilities, and independent ambulation with residual hemiparesis. **Conclusion.** Despite the severity of presentation, this case illustrates that timely surgical intervention combined with meticulous neurocritical care and structured rehabilitation can enable meaningful functional recovery. With appropriate patient selection and modern microsurgical techniques, even critically ill patients with pontine cavernomas may achieve favorable long-term outcomes.

**Key words**: Coma; Hemangioma, Cavernous; Hemorrhage; Pons; Young Adult; Diagnosis; Acute Care Surgery; Postoperative Care; Neurological Rehabilitation; Recovery of Function

**Sažetak**

**Uvod.** Kavernozni hemangiomi su benigne vaskularne malformacije sa prevalencijom procenjenom na 0,4–0,8%, dok kavernomi ponsa čine 14–30% intrakranijalnih kavernoma i predstavljaju veliki terapeutski izazov zbog bogatstva vitalnih nervnih puteva u moždanom stablu. Iako tehnički zahtevno, hirurško lečenje u pažljivo odabranim slučajevima može spasiti život pacijenta. **Prikaz slučaja.** Dvadesettrogodišnja žena sa višestrukim supratentorijalnim kavernomima inicijalno se lečila konzervativno zbog postojanja blagih simptoma. Devet meseci kasnije nađena je bez svesti nakon pojave iznenadne, jake glavobolje i povraćanja. Na prijemu je bila komatozna i zahtevala je hitnu intubaciju. Nalaz kompjuterizovane tomografije pokazao je opsežnu hemoragiju u regiji ponsa, a pregledom magnetne rezonance potvrđeno je značajno uvećanje kavernoma sa prisustvom akutnog krvarenja te kompresivnog efekta krvi. S obzirom na kritično stanje pacijentkinje načinjeno je hitno operativno lečenje u cilju evakuacije hematoma, uklanjanja kavernoma i dekompresije moždanog stabla. Zahvaljujući intenzivnoj postoperativnoj brizi i petomesečnoj neurorehabilitaciji pacijentkinja je postepeno napredovala sa povratkom refleksa gutanja, inicijacijom govora i značajnim poboljšanjem motorike. Na kontrolnom pregledu nakon godinu dana imala je potpuni ko-gnitivni oporavak i normalno je komunicirala, bila je pokretna uz rezidualnu hemiparezu. **Zaključak.** Uprkos težini kliničkog stanja ovaj slučaj pokazuje da pravovremena hirurška intervencija, pažljiva neurointenzivna nega i strukturisana rehabilitacija mogu omogućiti značajan oporavak. Uz pažljiv odabir pacijenata i upotrebu savremenih tehnika povoljan ishod se može postići čak i kod pacijenata u kritičnom stanju.

**Ključne reči**: koma; kavernozni hemangiom; krvarenje; pons; mlada osoba; dijagnoza; urgentna hirurgija; postoperativna nega; neurološka rehabilitacija; oporavak funkcije

## Introduction

Cavernous hemangiomas (CHs), also referred to as cavernous malformations, are benign vascular lesions composed of clusters of dilated, thin-walled capillary channels surrounded by hemosiderin deposits and gliotic tissue [1,2]. They are relatively rare, with an estimated prevalence of 0.4–0.8% in the general population, approximately 20% of which are associated with hereditary forms [1,3,4,5]. Cavernomas can occur anywhere within the central nervous system and demonstrate a broad clinical spectrum, rang-

✉ Corresponding author: dr Sara Azarić, E-mail: sara.azaric@gmail.com, jagos.golubovic@mf.uns.ac.rs

***Abbreviations***

| | |
|---|---|
| CHs | – cavernous hemangiomas |
| MRI | – magnetic resonance imaging |
| CT | – computed tomography |
| CTA | – computed tomographic angiography |
| DSA | – digital subtraction angiography |
| ICU | – intensive care unit |
| PEG | – percutaneous endoscopic gastrostomy |
| CN | – cranial nerve |
| GRE | – gradient recalled echo |
| SWI | – susceptibility weighted imaging |
| SEZ | – safe entry zone |

ing from incidental asymptomatic findings to severe neurological deficits depending on lesion location and the presence of hemorrhage [1,2,6].

Because these lesions are characterized by slow blood flow and low hemodynamic pressure, the overall risk of rupture is lower compared with other vascular malformations [1,2]. However, hemorrhage within eloquent or critical regions can result in significant neurological impairment even when bleeding volume is relatively small [2,6]. Nearly half of cases (approximately 47%) are detected incidentally during magnetic resonance imaging (MRI), which remains the gold standard due to its superior soft-tissue contrast. Computed tomography (CT) is primarily used for detecting acute hemorrhage, while digital subtraction angiography (DSA) may aid in differentiating cavernomas from other vascular malformations [7,8].

Brainstem cavernomas account for approximately 14–30% of all intracranial cavernous malformations, with 62–70% located within the pons [7,9–11]. Owing to the dense concentration of critical neural pathways and nuclei within the pontine region, even minor hemorrhages can lead to severe neurological deficits [11]. Management requires careful balancing of the significant risks associated with surgical intervention against the potentially devastating consequences of recurrent or progressive hemorrhage [9,11].

Rupture of a pontine cavernoma presenting with deep coma is rare and typically associated with poor prognosis if not treated emergently [12]. Given the limited literature describing favorable outcomes in such severe presentations, individual cases provide valuable insights for guiding clinical decision-making [9,13]. Here, we report a young female patient admitted in a comatose state due to a ruptured pontine cavernoma who achieved remarkable neurological recovery following urgent surgical intervention.

## Case Report

*Patient Presentation*: A 23-year-old woman with a history of multiple small supratentorial cavernomas and well-controlled epilepsy presented to the emergency department with bilateral hand paresthesia, diplopia, and right eye strabismus. CT/CTA revealed multiple hyperdense lesions, including a pontine lesion measuring 15 x 16 x 15 mm **(Figure 1).** MRI demonstrated the characteristic "popcorn-like" appearance with a hemosiderin rim. Digital subtraction angiography (DSA), performed to exclude associated developmental venous anomalies, was negative. Given mild neurological symptoms and the patient's otherwise good clinical condition, conservative management was initially adopted. Serial follow-up MRI studies demonstrated gradual reduction in lesion size **(Figure 2).**

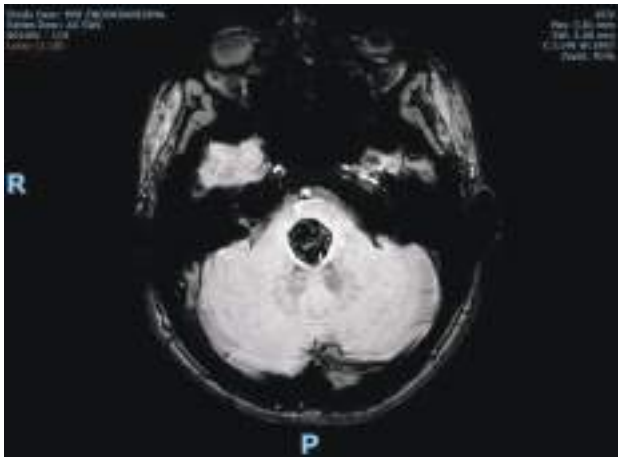


**Figure 1**. MRI- SWI weighted sequence – first hemorrhage

Nine months later, the patient was emergently readmitted after sudden onset of severe headache, vomiting, and loss of consciousness, without preceding trauma. On arrival, she showed no purposeful motor responses, no eye opening, and only minimal brainstem reflexes, corresponding to a Glasgow Coma Scale score of 3 (GCS3). Pupils were reactive; however, immediate endotracheal intubation was required.

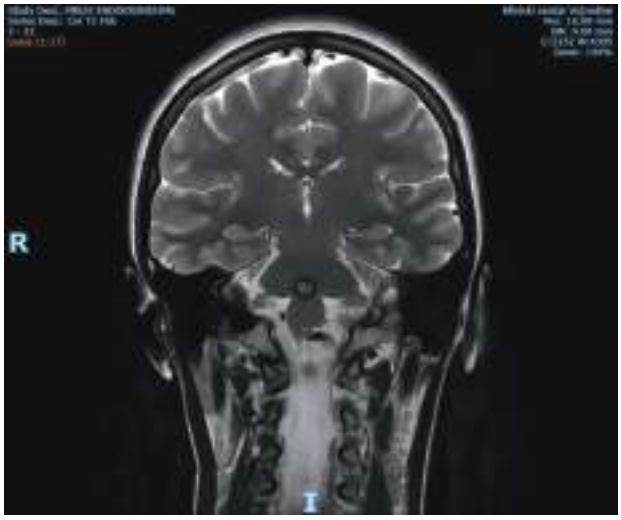


**Figure 2.** MRI T2 FSE – follow-up MRI between the two hemorrhagic events

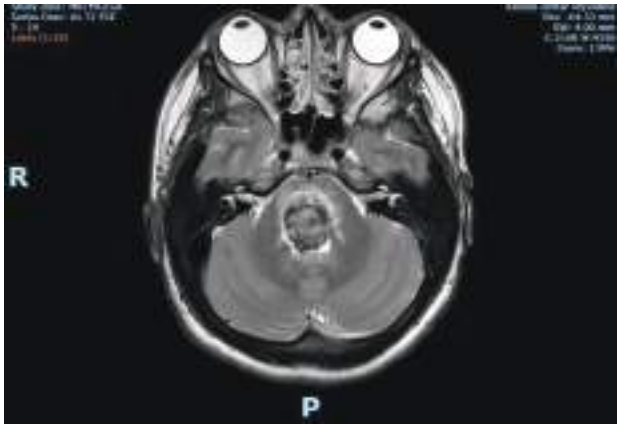


**Figure 3.** MRI T2-weighted sequence – rehemorrhage

*Initial Investigations:* Following stabilization, urgent non-contrast CT imaging revealed centrally located hyperdense pontine hemorrhage causing significant mass effect on the fourth ventricle, indicating a life-threatening condition with high risk of acute obstructive hydrocephalus. Emergency MRI confirmed enlargement of the pontine lesion to 22×27×21 mm, with radiological evidence of recent hemorrhage extending into the dorsal pons **(Figure 3).** MR angiography showed no additional vascular abnormalities.

*Surgical Intervention:* Given the patient's critical neurological status and imaging findings, emergency microsurgical intervention was undertaken to evacuate the hematoma, remove the cavernoma, and relieve brainstem compression.

The patient was positioned prone in a Mayfield head holder for a posterior fossa approach. A midline suboccipital craniotomy was performed to expose the cerebellar vermis and cisterna magna. After dural opening, cerebrospinal fluid was gently released from the basal cisterns to reduce cerebellar tension.

A telovelar approach was used to access the fourth ventricle. Due to cerebellar swelling, partial resection of the inferior vermis was required to achieve adequate exposure. The floor of the fourth ventricle demonstrated bluish discoloration and bulging in the region corresponding to the dorsal pontine cavernoma identified on MRI.

Using microsurgical technique, the suprafacial triangle was selected as the safe entry zone. Continuous intraoperative neurophysiological monitoring, including facial nerve and long-tract monitoring, was utilized. The cavernoma and associated hematoma were carefully evacuated while minimizing traction on surrounding pontine tissue and maintaining meticulous hemostasis **(Figure 4).** The surgical field was irrigated, fourth ventricle outlets were inspected for patency, and standard dural and bone closure was performed.

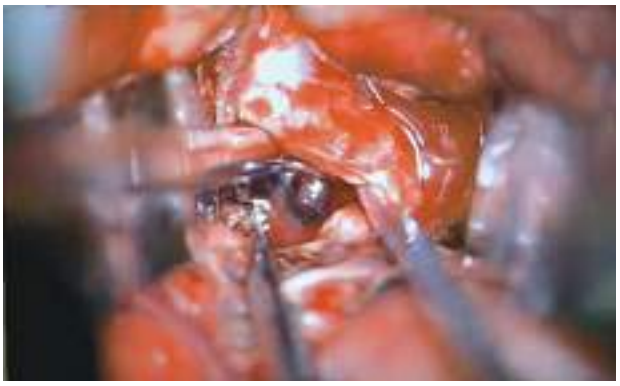

**Figure 4.** Intraoperative finding – SEZ approach and evacuation of hematoma

*Postoperative Course in the ICU:* The patient was transferred to the ICU under mechanical ventilation and sedation. Immediate postoperative CT confirmed complete lesion removal, adequate hematoma evacuation, and decompression of the brainstem without new hemorrhage **(Figure 5).** During the first 24–48 hours, comprehensive neurocritical care was provided. Although initially comatose, the patient gradually demonstrated improvement in brainstem reflexes. Due to impaired swallowing and airway protection, tracheostomy and percutaneous endoscopic gastrostomy (PEG) placement were performed for respiratory and nutritional support.

The postoperative course was complicated by episodes of dysautonomia, including tachycardia, blood pressure fluctuations, and temperature instability, likely related to central autonomic dysfunction following brainstem injury. These were managed with supportive pharmacologic therapy.

Over a two-week period, consciousness improved progressively and sedation was tapered. Respiratory function gradually recovered, allowing successful ventilator weaning after approximately six weeks.

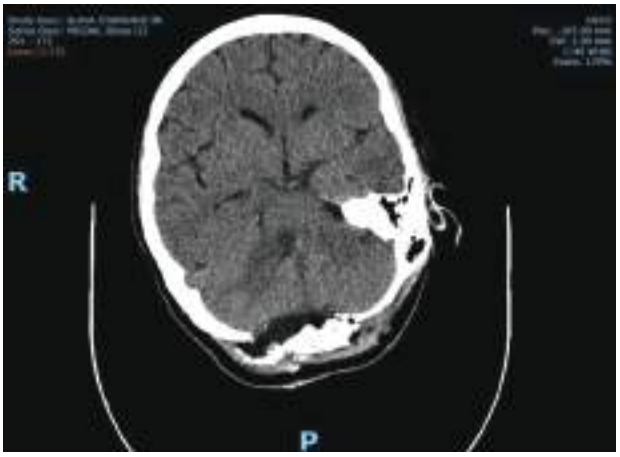


**Figure 5.** CT on the first postoperative day – complete evacuation of hematoma and decompression

*Neurological Rehabilitation:* Following medical stabilization, the patient was transferred to an in-hospital neurorehabilitation unit approximately 6–7 weeks after hemorrhage. At that time, she was awake and intermittently alert, with dysphagia and severe tetraparesis (left side more affected), consistent with corticospinal tract involvement from the pontine lesion. Cognitive function remained preserved, and communication was initially achieved through gestures.

She underwent intensive physiotherapy and speech/swallow therapy. By the fourth month, she was able to sit and stand with assistance for approximately 17 minutes and demonstrated progressive improvement in swallowing function. At discharge, she was able to initiate speech by occluding the tracheostomy and tolerated soft oral intake with supervision, while PEG feeding remained necessary for supplemental nutrition.

*Follow-up and outcomes:* After approximately five months of hospitalization, the patient was discharged home with structured outpatient rehabilitation. Family members received training in tracheostomy care and PEG feeding, and a multidisciplinary follow-up was arranged.

At one year follow-up, the tracheostomy tube had been successfully removed following recovery of airway reflexes and adequate respiratory function. Swallowing function improved to near-normal levels, allowing maintenance of body weight on a regular diet with minor texture modifications.

The patient was alert, cognitively intact, and able to communicate effectively with only minor speech difficulties. Residual deficits included moderate left-sided hemiparesis, facial weakness, and mild right lateral gaze palsy consistent with abducens nerve involvement. Coordination had significantly improved compared with early postoperative status.

## Discussion

We conducted a focused review of the literature regarding similar clinical presentations and current management strategies for pontine cavernomas. Cavernous malformations typically present at a younger age compared with hypertensive intracerebral hemorrhages, most frequently affecting individuals between the second and fourth decades of life, with some studies suggesting a slight female predominance [6,10,14]. The annual hemorrhage risk for previously unruptured cavernomas is relatively low, estimated at approximately 2.7–5% per lesion per year; however, following an initial bleed, the risk of re-hemorrhage increases significantly, reaching 21–30% per lesion annually [9,10]. This elevated rebleeding risk, combined with cumulative neurological injury from repeated hemorrhages, represents a major argument in favor of surgical treatment of accessible brainstem cavernomas, particularly in younger patients with long life expectancy [9,15].

Unlike hypersensitive pontine hemorrhages, which are often associated with high mortality and limited surgical options, hemorrhages secondary to cavernous malformations represents a distinct entity in which the underlying bleeding source may be definitely removed through microsurgical resection [9,12].

Consequently, carefully selected cases may benefit from aggressive surgical management despite the inherent risks associated with brainstem surgery.

*Diagnostic and Surgical Considerations:* In the emergency setting, non-contrast CT remains essential for rapid identification of acute hemorrhage and hydrocephalus. MRI (T2, T2, GRE, and SWI sequences) provides definitive diagnosis and detailed anatomical characterization necessary for surgical planning [8,15,16].

The decision to operate on pontine cavernomas requires careful risk-benefit analysis. However, in patients presenting with severe neurological deterioration or coma, surgical intervention may represent the only realistic chance for survival or meaningful functional recovery [9,13]. Favorable surgical candidates often include lesions that reach a pial or ependymal surface [17]. Trajectory planning is critical. Although techniques such as the two-point method can assist in minimizing retraction and defining optimal surgical corridors, established brainstem safe-entry zones (SEZs) remain the preferred strategy to reduce injury to eloquent neural structures [10,18]. Within the pontine portion of the fourth ventricle, there are three principal SEZs include the suprafacial and infrafacial triangles as well as the median sulcus [20]. Nevertheless, any entry into the pons carries substantial risk of long-tract and cranial nerve injury [19,20].

*Postoperative course:* Paroxysmal sympathetic hyperactivity is reported in approximately 8–33% of patients with severe brain injury and is generally managed with supportive and symptomatic treatment [21,22]. Furthermore, multiple studies emphasize the importance of early, specialized, and prolonged neurorehabilitation, as patients frequently experience dysphagia, ataxia, dysarthria, paresis, and diplopia, all of which significantly impact functional independence and quality of life. Despite the complexity of recovery, a multidisciplinary approach can result in meaningful functional improvement [9–11,23,24].

## Conclusion

Ruptured pontine cavernomas represent life-threatening neurosurgical emergencies that challenge both

surgical decision-making and neurocritical care management. Although emergency brainstem surgery carries substantial risks, selected cases may achieve favorable outcomes.

This case contributes to the limited body of literature demonstrating that meaningful recovery is possible even in patients presenting in deep coma following brainstem cavernoma hemorrhage. While neurological recovery is typically prolonged and gradual, significant functional gains may occur over months to years.

For clinicians, this case underscores an important message: severe initial presentation should not automatically preclude aggressive treatment in young patients with surgically accessible pontine cavernomas. When anatomical conditions permit safe access and comprehensive perioperative care is available, surgical intervention may offer the potential for substantial neurological recovery.

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Rad je primljen 21. XI 2025.
Recenziran 11. II 2026.
Prihvaćen za štampu 11. II 2026.
BIBLID.0025-8105:(2025):LXXVIII:9-12:312-316.

## REGISTAR ZA 2025. GODINU

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# INDEKS KLJUČNIH REČI

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61:061(497.113)

**MEDICINSKI pregled :** časopis Društva lekara Vojvodine Srpskog lekarskog društva = Medical review : journal of the Society of physicians of Vojvodina of the Medical Society of Serbia / glavni i odgovorni urednik Ljilja Mijatov Ukropina. – God. 1, br. 1 (1948)- . – Novi Sad : Društvo lekara Vojvodine Srpskog lekarskog društva, 1948- (Novi Sad : Feljton). – 28 cm

Dvomesečno. – Drugo izdanje na drugom nedijumu: Medicinski pregled (Online) = ISSN 1820-7383

ISSN 0025-8105 = Medicinski pregled

COBISS.SR-ID 3138306

COBISS.SR-ID 331773959

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