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World Health Day (WHD) 2026, observed on April 7, highlights the key role of science and international cooperation in protecting global health. This year's WHD theme, "Together for Health. Stand with Science," emphasizes that evidence-based research, international collaboration, and reliable health information form the strongest foundation for building a safer and healthier future for all. WHD should also remind us to reflect on the well-being of healthcare professionals. Osteoarthritis is a common problem among healthcare workers. More on this topic can be found in the "Health personnel and knee osteoarthritis: April as a reminder of a neglected risk" (p. 203-207).

Svetski dan zdravlja (SDZ) 2026, koji se obeležava 7. aprila, ističe ključnu ulogu nauke i međunarodne saradnje u zaštiti globalnog zdravlja. Tema ovogodišnjeg SDZ, „Zajedno za zdravlje. Stanimo uz nauku," naglašava da su rezultati istraživanja zasnovanih na dokazima, međunarodna saradnja i pouzdano informisanje o zdravlju, najsnažniji temelj u izgradnji bezbednije i zdravije budućnosti za sve. SDZ bi trebalo da nas podseti i da razmislimo o dobrobiti zdravstvenih radnika. Osteoartritis je problem mnogih zdravstvenih radnika. Više o ovoj temi pročitajte u radu „*Zdravstveni radnici i osteoartritis kolena: april kao podsetnik na zanemareni rizik*" (str. 203-207).

I N F O C U S

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Health personnel and knee osteoarthritis: April as a reminder of a neglected risk

Zdravstveni radnici i osteoartritis kolena: april kao podsetnik na zanemareni rizik

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Abstract

Although often viewed as a condition of the general population, clinical observations indicate that a substantial proportion of knee-pain consultations due to osteoarthritis involve healthcare workers, suggesting a potential burden that exceeds expectations for age-matched adults. Existing research reports a high incidence of knee symptoms among healthcare workers, including a 47% prevalence of work-related knee musculoskeletal disorders in perioperative nurses. However, these studies focus on symptoms rather than diagnosed osteoarthritis, leaving the true burden of structural disease in this population understudied. Occupational demands such as prolonged standing, extensive walking, frequent pivoting, kneeling, squatting, and physically intensive patient handling impose ongoing stress that may accelerate joint degeneration. Increasing retirement age further extends years of exposure, increasing the risk of chronic musculoskeletal conditions. Despite this, knee osteoarthritis remains largely absent from occupational health and safety policies. Low-cost workplace interventions, such as structured movement breaks, brief strength exercises, and consistent access to assistive devices, represent promising approaches, even though current evidence remains limited, and further research is needed to confirm their preventive effect. Legislative measures, such as reduced working hours for older employees, may help mitigate cumulative strain. Emerging technologies, including robot-assisted patient handling, show the potential to reduce high-force exposures. Recognizing knee osteoarthritis as a preventable occupational health issue is essential for protecting the mobility, well-being, and professional longevity of the healthcare workforce.

Keywords:
age factors; health personnel; musculoskeletal diseases; occupational exposure; osteoarthritis, knee; risk assessment.

Apstrakt

Iako se često posmatra kao oboljenje opšte populacije, klinička zapažanja ukazuju na to da značajan deo pregleda zbog bola u kolenu usled osteoartritisa obuhvata upravo zaposlene u zdravstvu, što upućuje na moguće opterećenje koje prevazilazi očekivani nivo za odrasle osobe istog životnog doba. U postojećim istraživanjima navodi se visoka učestalost simptoma oboljenja kolena kod zdravstvenih radnika, uključujući prevalenciju od 47% za mišićno-skeletne poremećaje kolena povezanih sa poslom kod perioperativnih medicinskih sestara. Međutim, ova istraživanja se bave simptomima, a ne dijagnostikovanim osteoartritisom, ostavljajući nedovoljno ispitan stvarni teret strukturnog oboljenja u toj populaciji. Radne obaveze koje uključuju dugotrajno stajanje, intenzivno hodanje, često okretanje, klečanje, čučanje i fizički zahtevno zbrinjavanje bolesnika, nameću trajno opterećenje koje može ubrzati degeneraciju zgloba. Povećanje starosne granice za penzionisanje dodatno produžava godine izloženosti, povećavajući rizik od hroničnih mišićno-skeletnih oboljenja. Uprkos tome, osteoartritis kolena ostaje uglavnom odsutan iz politika zaštite na radu. Intervencije na radnom mestu čiji troškovi nisu veliki, poput struktuiranih pauza za kretanje, kratkih vežbi snage i dosledne upotrebe pomagala, predstavljaju obećavajuće pristupe, iako su trenutni dokazi ograničeni i potrebna su dalja istraživanja radi potvrde njihovog preventivnog efekta. Zakonom regulisane mere, poput skraćenog radnog vremena za starije radnike, mogu dodatno smanjiti kumulativno opterećenje. Nova tehnološka rešenja, uključujući pomoć robota u zbrinjavanju bolesnika, pokazuju potencijal za smanjenje izloženosti velikim silama. Prepoznavanje osteoartritisa kolena kao problema profesionalnog rizika koji se može sprečiti, ključno je za očuvanje pokretljivosti, dobrobiti i dugoročne radne sposobnosti zdravstvenog kadra.

Ključne reči:
životno doba, faktor; zdravstveno osoblje; mišićno-skeletne bolesti; profesionalna izloženost; osteoartritis, koleno; rizik, procena.

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Introduction

Knee osteoarthritis (OA) – KOA is rarely acknowledged as an occupational hazard, yet clinical practice shows that healthcare workers (HCWs) experience knee problems at rates that exceed expectations for their age and activity level [1–5]. A significant proportion of consultations for KOA involve hospital employees, revealing a burden that remains largely invisible in discussions about workforce wellbeing. Against this backdrop, April 7 – traditionally observed as World Health Day [6] – offers a timely opportunity to draw attention to overlooked occupational risks and to reconsider how health systems protect the musculoskeletal health of those who care for others.

The burden of knee osteoarthritis in medical personnel

KOA is often described as a condition of the general population [7], typically attributed to aging, obesity, or recreational overuse [8–10]. Yet, our clinical experience suggests a different pattern: among thousands of HCWs, knee pain is a frequent complaint, and the fact that so many affected individuals are themselves medical personnel indicates that occupational exposures may play a more substantial role than commonly assumed. The most common cause of chronic knee pain in people in their 50s is OA [11], and individuals with early KOA often report broader and more diffuse pain areas than those with normal knees or progressive disease [12]. Radiographic OA and its individual features are strongly associated with knee pain, reinforcing the clinical relevance of structural changes [13]. Despite these observations, current research does not yet clarify the true prevalence of KOA across healthcare settings.

Existing studies on musculoskeletal disorders in HCWs consistently report high rates of knee symptoms [2–5]. Hospital nurses experience knee complaints in nearly one quarter of cases [14], and nursing-home staff reports persistent knee pain even after the introduction of safe resident-handling programs intended to reduce physical strain [15]. A systematic review and meta-analysis of perioperative nurses found a 47% prevalence of work-related knee musculoskeletal disorders, underscoring the substantial biomechanical demands in surgical environments [16]. However, these investigations primarily address pain and symptoms rather than diagnosed OA, leaving the true burden of structural joint disease in healthcare personnel largely unexamined. Given the high physical demands and cumulative joint loading characteristic of healthcare work, this knowledge gap represents a significant and timely concern.

Occupational risk factors in health workers

Occupational physical activity is a modifiable risk factor for both radiographic and symptomatic KOA [17, 18]. The physical demands of healthcare work create a unique and potent combination of exposures that accelerate knee joint degeneration. Long periods of standing during rounds, procedures, and patient care increase compressive forces across the joint, while extensive walking on hard flooring adds repetitive impact. Frequent pivoting and directional changes introduce rotational stress, and tasks such as kneeling, squatting, and working in low positions are routine in nursing, physiotherapy, emergency care, and operating rooms. Performed repeatedly over the years, these activities contribute to cumulative joint loading that accelerates cartilage wear and increases the likelihood of OA [19].

Patient handling remains one of the most physically demanding aspects of healthcare work. Lifting, repositioning, and transferring patients often occur under time pressure, with limited staffing or inconsistent access to assistive devices. Even when equipment is available, workflow constraints may discourage its use. These conditions increase the likelihood of suboptimal mechanics, uneven load distribution, and sudden high-force movements that strain the knee joint. Over time, repeated exposures create a biomechanical environment conducive to joint degeneration.

At the opposite end of the occupational spectrum, administrative and diagnostic roles present a different but equally relevant risk pattern. Prolonged sitting [20], low step counts, and minimal movement variability – conditions also associated with OA risk [21] – reduce joint nutrition, promote muscle deconditioning, and impair neuromuscular control. Whether overloaded or under-moved, the knee joint pays the price.

Movement behavior in HCWs is paradoxical. Shifts demand high levels of occupational activity, yet off-hours are often marked by profound sedentary behavior driven by fatigue. This imbalance – intense loading without restorative movement – exacerbates symptoms and undermines long-term joint health [22, 23].

Retirement age and cumulative exposure: a structural challenge

The increasing retirement age further intensifies the long-term physical demands placed on HCWs. According to the Law on Pension and Disability Insurance of the Republic of Serbia [24], retirement conditions have changed substantially over the past decade. In 2015, women could retire at age 55 with 36 years and 4 months of insurance service, while men qualified at 55 with 40 years of service. These thresholds have progressively increased. In 2026, the full retirement age reaches 64 years for women and 65 for men, with a minimum of 15 years of insurance service. Alternatively, retirement is possible after completing 45 years of insurance service, regardless of age, while early retirement requires at least 40 years of service and a minimum age of 60.

For HCWs, these changes translate into additional years of cumulative exposure to physically demanding tasks. Prolonged exposure to standing, walking, lifting, kneeling, and performing repetitive patient-handling activities over such extended working lives substantially increases the risk of chronic musculoskeletal conditions [25], including KOA. The mismatch between the increasing retirement age and unchanged physical workload creates a structural vulnerability:

workers are expected to remain fully functional in roles that impose continuous biomechanical stress well into their 60s [26].

Epidemiological evidence shows that women bear a higher burden of KOA, with incidence peaking in their 50s and disability burden reaching its highest levels in later decades [27]. Under Serbia's current retirement policy, women remain in physically demanding roles precisely during years of the greatest KOA vulnerability, amplifying their occupational health risk.

This legal context underscores the urgency of recognizing KOA as an occupational health issue. As working life extends, cumulative joint load increases, making prevention, early detection, and workplace adaptation essential for sustaining the healthcare workforce.

Why this issue demands attention now

The consequences of KOA extend far beyond individual discomfort. Pain, reduced mobility, and functional limitations directly impair work ability, productivity, and career longevity. In already strained health systems, where staffing shortages and burnout are widespread, musculoskeletal conditions contribute to absenteeism, presenteeism [28], and premature exit from the workforce. These outcomes disrupt patient flow, increase the workload for remaining staff, and compromise continuity of care. Protecting the musculoskeletal health of HCWs is therefore not only a clinical priority but a strategic requirement for maintaining a resilient and sustainable workforce.

Despite the magnitude of the problem, KOA remains largely absent from occupational health policies and institutional well-being programs. Many hospitals prioritize back injuries, needlestick prevention, or psychosocial stress, while joint health receives comparatively little attention. This gap reflects a broader tendency to view OA as an inevitable consequence of aging rather than a preventable occupational condition. Yet, available evidence demonstrates that workplace factors substantially shape risk and that targeted interventions can meaningfully reduce joint strain [29, 30].

Strategies to reduce knee joint load and preserve work ability

Low-cost, workplace-based strategies have positive effects on improving employee health status [31] and offer practical opportunities for prevention and symptom management. Ergonomic improvements can reduce mechanical stressors [32], while structured movement breaks integrated into shifts can counteract prolonged standing and reduce cumulative load [33]. Brief strength [34] or mobility sessions – even as short as five minutes – can improve neuromuscular control, enhance joint stability, and reduce pain. Still, the broader evidence base for workplace-based prevention and management of knee pain remains insufficient, leaving institutions without clear guidance for effective preventive practice or policy design [35]. Supportive footwear can decrease impact forces during walking, while consistent access to assistive devices for patient handling can reduce high-force exposures [36]. These interventions require minimal resources and can be implemented within existing workflows, making them particularly relevant for health systems operating under budgetary constraints.

Although robotics is not a low-cost solution, findings by Brinkmann et al. [37] demonstrate the feasibility of collaborative robot-assisted patient handling and highlight the need for future individualized intervention programs aimed at reducing physical burden in care.

Early screening for knee symptoms and functional limitations can help identify workers at risk before structural damage progresses. Simple assessments of strength, balance, and movement patterns can guide individualized recommendations and prevent further deterioration. Educational initiatives that promote joint-friendly movement strategies, ergonomic awareness, and recovery practices can empower HCWs to protect their own musculoskeletal health. Importantly, these efforts should not place responsibility solely on individuals; institutional policies must support and reinforce healthy practices.

Research consistently shows that reduced working hours can help preserve work ability across a range of occupations [38–40]. A qualitative study by Gyllensten et al. [38] found that nurses working shorter shifts reported less fatigue, greater energy, and improved patient interaction. These findings are supported by a randomized controlled trial by Schiller et al. [39] which demonstrated that work-time reduction enhances recovery and sleep quality without increasing total workload. A systematic review by Voglino et al. [40] further confirms that shorter working hours improve health outcomes and reduce sickness absence across diverse occupational groups. These scientific insights align with recent policy developments in Slovenia, where the 2026 "80–90–100" model enables workers aged 58+ or with at least 35 years of service to reduce working hours while maintaining full pension contributions [41]. This combination of scientific evidence and implemented policy demonstrates that structured work-time reduction is a viable strategy to preserve the functional capacity of older workers, particularly in physically demanding sectors such as healthcare.

A call for recognition and action

World Health Day, observed on April 7, provides a timely public health context for advancing this discussion. While global health observances often highlight broad themes such as universal health coverage or chronic disease prevention, they also remind us to reflect on the well-being of the healthcare workforce itself. KOA may not be a headline topic, but it is a daily reality for many health professionals. Recognizing it as a legitimate occupational risk is a necessary step toward addressing the physical demands of healthcare work and ensuring that those who provide care can continue to do so safely and sustainably.

The path forward requires a shift in perspective. KOA should not be viewed as an unavoidable consequence of aging or personal lifestyle choices. In many cases, it is a preventable and modifiable occupational health issue. By acknowledging the role of workplace exposures, implementing practical interventions, and integrating evidence-based strategies such as reduced working hours for older workers, healthcare systems

can meaningfully reduce joint strain and support the long-term well-being of their workforce.

Conclusion

Healthcare workers dedicate their careers to improving the health of others. Ensuring that their own joint health is protected is both an ethical responsibility and a strategic investment in the future of healthcare. Every occasion should serve as a reminder that this issue can no longer be overlooked. Recognizing and addressing knee osteoarthritis as a neglected occupational risk is essential for safeguarding the mobility, well-being, and professional longevity of those who sustain the health of our communities.

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Neutrophil gelatinase-associated lipocalin as a predictor of treatment outcomes in primary glomerulonephritis

Lipokalin udružen sa neutrofilnom gelatinazom kao prediktor ishoda lečenja primarnog glomerulonefritisa

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Abstract

Background/Aim. Biomarkers for predicting disease course could facilitate treatment selection in primary glomerulonephritis (PGN). Data on the role of neutrophil gelatinase-associated lipocalin (NGAL) in PGN are limited. The aim of this study was to evaluate the significance of NGAL in predicting treatment outcomes in PGN. **Methods.** The study included a total of 60 PGN patients followed between 2012 and 2024. At diagnosis, serum NGAL (sNGAL) and urinary NGAL (uNGAL) were measured. Renal function parameters (serum creatinine, proteinuria) and disease outcome–development of end-stage renal disease (ESRD)–were assessed at baseline, after 5 years, and at the end of the follow-up period. The association between NGAL and clinical outcomes was analyzed using appropriate statistical tests. **Results.** At baseline, median sNGAL and uNGAL levels were 154.71 ng/mL and 13.94 ng/mL, respectively. During a median follow-up of 112 months, 8.33% of patients were lost to follow-up, and 20% developed ESRD. Patients who developed ESRD had higher sNGAL levels (p = 0.027). Using sNGAL, ESRD was fairly predictive (AUC = 0.709; p = 0.036), and sNGAL was associated with time-to-ESRD (Kaplan-Meier analysis, $p < 0.001$). The group with the highest sNGAL showed the lowest 5-year renal survival. Patients with stable or improved estimated glomerular filtration rate (eGFR) had higher uNGAL/creatinine ratio values (p = 0.049). Changes in proteinuria correlated negatively with sNGAL ($p < 0.001$) and uNGAL (p = 0.005). **Conclusion.** In PGN, sNGAL could be a predictor of ESRD development, potentially reflecting its pro-fibrotic activity. In contrast, the correlation between NGAL levels and change in proteinuria, as well as the associations between higher uNGAL/creatinine ratios and improved eGFR, suggest a complex and potentially protective role of NGAL in disease progression.

Keywords:
biomarkers; glomerulonephritis; kidney failure, chronic; lipocalins; treatment outcome.

Apstrakt

Uvod/Cilj. Biomarkeri za predviđanje toka bolesti mogli bi da olakšaju izbor terapije primarnog glomerulonefritisa (PGN). Podaci o ulozi lipokalina udruženog sa neutrofilnom gelatinazom (*neutrophil gelatinase-associated lipocalin* – NGAL) u PGN su oskudni. Cilj rada bio je da se proceni značaj NGAL u predviđanju ishoda lečenja PGN. **Metode.** Istraživanjem je obuhvaćeno ukupno 60 obolelih od PGN, praćenih od 2012. do 2024. godine. Pri postavljanju dijagnoze određivani su serumski NGAL (sNGAL) i urinarni NGAL (uNGAL). Parametri bubrežne funkcije (serumski kreatinin, proteinurija) i ishod bolesti–razvoj terminalnog stadijuma bubrežne slabosti (*end-stage renal disease* – ESRD)–procenjivani su na početku praćenja, posle 5 godina i posle kompletnog perioda praćenja. Povezanost NGAL i kliničkih ishoda analizirana je korišćenjem odgovarajućih statističkih testova. **Rezultati.** Na početku, medijane nivoa za sNGAL i uNGAL iznosile su 154,71 ng/mL i 13,94 ng/mL, redom. Tokom medijane praćenja od 112 meseci, 8,33% bolesnika je izgubljeno iz praćenja, a 20% je razvilo ESRD. Bolesnici koji su razvili ESRD imali su više nivoe sNGAL (p = 0,027). Korišćenjem sNGAL, razvoj ESRD bio je solidno predvidljiv (AUC = 0,709; p = 0,036), a sNGAL je bio značajno povezan sa vremenskim periodom do razvoja ESRD (Kaplan-Meier analiza, $p < 0,001$). U grupi sa najvišim sNGAL petogodišnje preživljavanje bubrega bilo je najniže. Bolesnici sa stabilnom ili poboljšanom procenjenom stopom glomerularne filtracije (*estimated*

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glomerular filtration rate – eGFR) imali su više vrednosti odnosa uNGAL/kreatinin (p = 0,049). Promene u vrednostima proteinurije bile su u negativnoj korelaciji sa koncentracijama sNGAL (p < 0,001) i uNGAL (p = 0,005). **Zaključak.** Kod obolelih od PGN, sNGAL može biti prediktor razvoja ESRD, potencijalno odražavajući njegovu profibroznu aktivnost. Nasuprot tome, korelacija između nivoa NGAL i promene vrednosti proteinurije, kao i povezanost između viših vrednosti odnosa uNGAL/kreatinin i poboljšane eGFR, ukazuju na složenu i potencijalno protektivnu ulogu NGAL u progresiji bolesti.

Ključne reči:
biomarkeri; glomerulonefritis; bubreg, hronična insuficijencija; lipokalini; lečenje, ishod.

Introduction

Primary glomerulonephritis (GN) – PGN comprises a heterogeneous group of inflammatory kidney diseases. The main therapeutic goals are to prevent the onset and progression of renal damage and to reduce proteinuria. Despite current treatments, up to 60% of patients progress to end-stage renal disease (ESRD) within ten years [1]. The 5-year mortality rate ranges from 6% to 33% among patients with nephrotic syndrome [2]. Although percutaneous renal biopsy remains the diagnostic gold standard for GN, it is an invasive procedure with limited applicability in certain cases. There is a need to identify reliable biomarkers that can facilitate GN diagnosis. Biomarkers capable of predicting PGN course could enable individualized treatment, avoiding unnecessary exposure to intensive therapies while ensuring timely intervention for high-risk patients. Most biomarkers studied in PGN are not routinely used in clinical practice [3]. Neutrophil gelatinase-associated lipocalin (NGAL), a 25-kilodalton low-molecular-weight glycoprotein, is a well-established nephrology biomarker [4]. In humans, NGAL is primarily detected in neutrophils [5, 6]. It is also found in various tissues, including the renal tubules, which release NGAL following injury [6, 7]. Beyond glomerular damage, tubulointerstitial changes significantly influence PGN outcome. Renal mesangial cells possess NGAL receptors and can produce NGAL in response to inflammation [8]. NGAL regulates cellular processes, including differentiation, proliferation, migration, and apoptosis [6, 9].

The blood of healthy individuals contains small amounts of NGAL [10]. Serum NGAL (sNGAL) and urinary NGAL (uNGAL) increase during PGN, through multiple mechanisms [4, 5, 8, 11, 12]. Neutrophils, the main source of NGAL, infiltrate the kidneys during active disease. Glomerular basement membrane (GBM) damage leads to increased filtration and loss of sNGAL [5, 12]. Prolonged proteinuria saturates the cubilin-megalin transport system, responsible for NGAL uptake, thereby reducing reabsorption. NGAL production is increased in renal and extrarenal tissues under chronic stress induced by proteinuria and cytokine stimulation [4, 5]. Published data suggest correlations of NGAL with residual renal function, serum creatinine (Cr), and proteinuria [4, 5, 11], supporting its potential role in PGN diagnosis and monitoring.

The aim of this study was to evaluate the association between NGAL and renal function parameters in PGN, and to investigate whether baseline NGAL can predict disease course and outcomes of PGN.

Methods

Study population and design

This single-center observational study included 60 PGN patients, enrolled between January 2012 and January 2015. The study was conducted in compliance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the University Clinical Center of Vojvodina, Serbia (No. 00–209, from June 14, 2024). Informed consent was obtained from all participants. This study represents a continuation of a prospective investigation conducted as a part of a dissertation, with a follow-up of 6–25 months [13].

Inclusion criteria were as follows: age > 18 years, percutaneous renal biopsy-confirmed PGN, absence of prior disease-specific treatment, and willingness to participate in the study. Exclusion criteria included the following: secondary GN, lack of renal biopsy confirmation, pre-existing chronic kidney disease (CKD) of other etiology, malignancy, acute infection, and severe hepatic or cardiac failure.

Established diagnostic guidelines and standardized protocols were employed to diagnose PGN and to conduct a percutaneous renal biopsy. Demographic data and information on ESRD development–including the duration in months from diagnosis to the predefined endpoint–were extracted from medical records. Five patients who were lost to follow-up after 6 months were included only in baseline analyses and excluded from subsequent calculations. The remaining patients were categorized into groups according to the specified endpoint, and these groups were subsequently compared with respect to the monitored parameters.

Follow-up assessments were conducted at two time points: five years after diagnosis and at each patient's maximum follow-up, defined as the last available clinical evaluation up to March 2024. The primary endpoint was progression of renal failure to ESRD.

Patient stratification

Results of laboratory tests (serum Cr and proteinuria) were recorded at diagnosis, and on every follow-up point. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Changes in eGFR and proteinuria from baseline were assessed, along with the average annual change in eGFR.

Patients were categorized into groups based on the annual eGFR changes during follow-up. Patients who were lost to follow-up, died within the first year, or lacked a final serum Cr were excluded from this analysis. Group 1 included patients who showed an improvement in eGFR or had an annual eGFR decline of less than 1.5 mL/min/1.73m^2. Group 2 included patients with an annual eGFR decline of more than 1.5 mL/min/1.73m^2. The groups were subsequently compared.

For Kaplan-Meier survival analysis, patients were divided into four groups according to the sNGAL interquartile range (IQR) values: 1) < IQR1, 2) IQR1–IQR2, 3) IQR2–IQR3, and 4) > IQR3.

Laboratory analysis

At diagnosis, blood and urine samples were collected for measurement of sNGAL, uNGAL, and urinary Cr. Following centrifugation, samples were stored at -80 °C until analysis.

Concentrations of sNGAL and uNGAL were measured using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique. Original microplates incorporating monoclonal antibodies to NGAL (R&D Systems, Inc., Minneapolis, USA) were used. Results were read with a Multiskan MCC 340 ELISA reader. Serum samples were diluted at a ratio of 1 : 20, whereas urine samples were analyzed undiluted. Readings were performed at a wavelength of 450 nm. Concentrations were determined from a linear regression curve based on manufacturer-provided standards. For sNGAL, results were multiplied by a factor of 20. Values are expressed in ng/mL. The uNGAL/Cr ratio, expressed in ng/mg, was calculated to account for the influence of renal failure, using the following formula:

$$\frac{\text{uNGAL}}{\text{Cr}} = \frac{\text{urinary NGAL}}{\text{urinary creatinine}}$$

Statistical analysis

An Excel database was created specifically for this study. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Variables with non-normal distributions were reported as medians with IQR. The Wilcoxson rank-sum test was used to compare independent groups of continuous variables, while paired samples were analyzed using the paired Wilcoxson rank-sum test (data with non-normal distribution). Categorical variables were compared using Fisher's exact test. The correlation

Table 1

Monitored variables at baseline, 5-year follow-up, and at the final follow-up

Variables at time points	Median (IQR)
Baseline (n = 60)	
sNGAL	154.71 (115.65–216.53)
uNGAL	13.94 (11.63–15.48)
uNGAL/creatinine	21.88 (12.20–28.97)
creatinine	75.5 (61.0–109.5)
eGFR	93.5 (64.5–108.5)
proteinuria	6,237 (3,196–12,161.5)
5-year follow-up (n = 40)	
creatinine	85 (75.0–114.5)
eGFR	81 (54.5–97.5)
Δ eGFR	-12 (-33.5–3.5)
proteinuria	358.15 (132.5–1349.5)
Δ proteinuria	-4,962.5 (-10,348.5– -2271.5)
Total follow-up (n = 36)	
creatinine	102.5 (83.5–128.0)
eGFR	74 (44.5–85.0)
Δ eGFR	-23 (-35.5– -7.0)
annual Δ eGFR	-2.54 (-4.21– -0.895)
proteinuria	190 (69.0–749.0)
Δ proteinuria	-4,962.5 (-12,242.5– -1,453)

IQR – interquartile range; n – number of patients included in analysis; sNGAL – serum neutrophil gelatinase-associated lipocalin (NGAL); uNGAL – urinary NGAL; eGFR – estimated glomerular filtration rate; Δ eGFR – change in eGFR from baseline; Δ proteinuria – change in proteinuria from baseline.
***Note*: Units of measurement are given as ng/mL for sNGAL and uNGAL; ng/mg for uNGAL/creatinine; μmol/L for creatinine; mL/min/1.73 m^2 for eGFR and Δ eGFR; mg/day for proteinuria and Δ proteinuria.**

between NGAL levels and monitored parameters was assessed using Spearman's correlation coefficient. The Kaplan-Meier curve was used to visualize time-to-ESRD, stratified by sNGAL levels. Additionally, the odds ratio (OR) for ESRD development was calculated for these four groups. The ability of NGAL to discriminate between ESRD developers and those who remained dialysis-independent was evaluated using logistic regression. Results were presented using receiver operating characteristic (ROC) curves. Binomial logistic regression analyses were used to assess the discriminative ability of multivariate models in predicting renal survivor. All statistical tests were two-tailed, with a significance threshold set at $p < 0.05$. Statistical analysis was performed using RStudio (version 2023.03.1 + 446 "Cherry Blossom" Release) and Jamovi (version 2.6.26).

Results

The baseline median age of the 60 included patients was 53 years (IQR 18–77). Data regarding baseline characteristics, 5-year, and the final follow-up are presented in Table 1. Patients who died or became dialysis-dependent during the monitoring period were excluded from analyses at both follow-up time points.

A total of 34 (56.67%) patients had proliferative PGN, and 26 (43.33%) had non-proliferative PGN. Representation of different PGN subtypes is presented in Figure 1. There was no difference between proliferative and non-proliferative GN in sNGAL ($p = 0.445$, U statistic = 390, Effect size = -0.118), uNGAL ($p = 0.331$, U statistic = 376, Effect size = -0.149), or uNGAL/Cr ($p = 0.662$, U statistic = 412, Effect size = - 0.068).

When comparing different PGN subtypes using multiple comparisons analysis, no significant difference in uNGAL ($p = 0.652$, $F = 0.698$) or sNGAL ($p = 0.087$, $F = 1.97$) was observed.

However, rapidly progressive GN patients had significantly higher sNGAL compared to mesangioproliferative GN patients [$p = 0.039$, mean difference (MD) = -134, 95% confidence interval (CI): 40.25–227.75], and membranous nephropathy patients ($p = 0.025$, MD = 153.7, 95% CI: 53.25–254.15). The groups differed in uNGAL/Cr ($p = 0.021$, $F = 2.74$). Membranoproliferative GN patients had higher uNGAL/Cr compared to mesangioproliferative GN patients ($p = 0.044$, MD = 17.3, 95% CI: 3.8–30.8).

Five (8.33%) patients were lost to follow-up 6 months after diagnosis and were excluded from further analyses. The remaining patients were followed for a median of 112 months (IQR 67–124).

Table 2 summarizes the correlations between NGALs and the monitored variables at baseline and at two follow-up time points. At baseline, sNGAL and uNGAL correlated directly with serum Cr levels and negatively with eGFR. Proteinuria correlated positively with both NGAL measures; however, the correlation with sNGAL showed only a trend toward significance ($p < 0.1$) and did not reach statistical significance ($p < 0.05$). Over the entire follow-up, uNGAL/Cr correlated directly with both absolute and annual changes in eGFR, while uNGAL demonstrated a near-significant positive correlation with eGFR change. Change in proteinuria correlated negatively with both NGALs at the 5-year checkpoint and across the entire observation period.

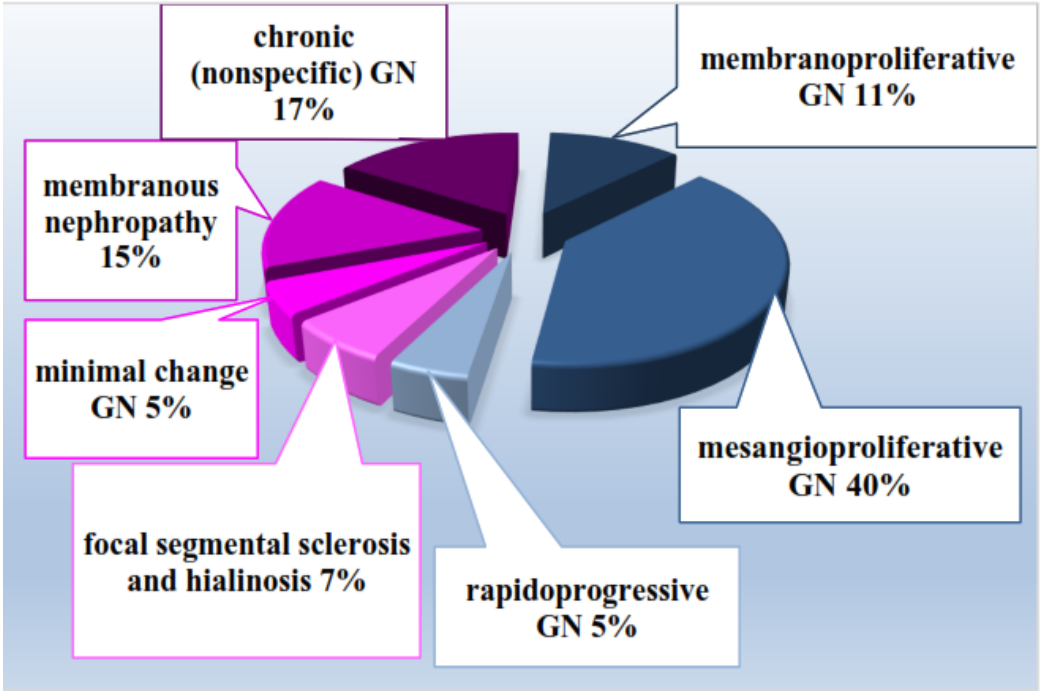

Fig. 1 – Representation of different primary glomerulonephritis (GN) subtypes.

Table 2

Correlations between NGAL and monitored variables

Variables at time points	sNGAL		uNGAL		uNGAL/Creatinine	
	p-value	*r*	*p*-value	*r*	*p*-value	*r*
Baseline						
age	0.759	-0.040	0.686	-0.053	0.381	-0.115
creatinine	< 0.001	0.510	0.047	0.258	0.270	0.145
eGFR	< 0.001	-0.431	0.046	-0.258	0.149	-0.189
proteinuria	0.069	0.237	0.018	0.306	0.701	0.050
5-year follow-up						
creatinine	0.041	0.325	0.660	0.072	0.698	0.063
eGFR	0.082	-0.279	0.840	-0.033	0.614	-0.082
Δ eGFR	0.817	0.038	0.207	0.204	0.065	0.295
proteinuria	0.548	-0.098	0.805	0.040	0.621	-0.081
Δ proteinuria	0.002	-0.470	0.006	-0.424	0.480	-0.115
Total follow-up						
creatinine	0.178	0.229	0.730	0.060	0.670	0.074
eGFR	0.480	-0.122	0.921	-0.017	0.651	-0.078
Δ eGFR	0.240	0.201	0.052	0.322	0.048	0.327
annual Δ eGFR	0.385	0.149	0.164	0.237	0.023	0.376
proteinuria	0.883	-0.025	0.838	0.035	0.518	0.111
Δ proteinuria	< 0.001	-0.541	0.005	-0.459	0.428	-0.136
time to ESRD	0.528	-0.203	0.914	-0.035	0.683	-0.133

NGAL – neutrophil gelatinase-associated lipocalin; sNGAL – serum NGAL; uNGAL – urinary NGAL; eGFR – estimated glomerular filtration rate; Δ eGFR – change in eGFR from baseline; annual Δ eGFR – average annual change in eGFR; Δ proteinuria – change in proteinuria from baseline; ESRD – end-stage renal disease.

Table 3

NGAL levels and ESRD development at two follow-up periods

Variables at time points	n	sNGAL	uNGAL	uNGAL/Creatinine
5-Year follow-up				
no ESRD	44	144.3 (100.2)	14 .0 (4.0)	19.4 (14.6)
ESRD	11	217.9 (127.7)	14.1 (2.5)	23.0 (28.8)
p		0.068	0.860	0.411
U statistic		155	233	202
effect size *r*		0.360	-0.037	0.165
Final follow-up				
no ESRD	43	138.2 (98.7)	14.1 (4.1)	21.5 (14.8)
ESRD	12	222.5 (117.1)	13.6 (2.3)	22.6 (30.3)
p		0.027	0.695	0.802
U statistic		150	238	245
effect size *r*		0.419	-0.077	0.050

NGAL – neutrophil gelatinase-associated lipocalin; ESRD – end-stage renal disease; sNGAL – serum NGAL; uNGAL – urinary NGAL.

Values are given as median (interquartile range).

***Note*: For units of measurement performed, see Table 1.**

Twelve (20%) patients developed ESRD, with the median time from diagnosis to ESRD of 38 months (IQR 19.5–47.5).

Patients were stratified according to renal survival at two follow-up time points. Baseline levels of sNGAL, uNGAL, and uNGAL/Cr were compared between groups (Table 3). Patients who progressed to ESRD had significantly higher baseline sNGAL than those who remained dialysis-independent. This difference was evident at the 5-year follow-up time point and reached statistical significance after completion of the follow-up period.

Four groups were created based on sNGAL IQR values: 1) sNGAL < 115.65 ng/mL, 2) sNGAL 115.66–154.71 ng/mL, 3) sNGAL 154.72–216.53 ng/mL, and 4) sNGAL > 216.53 ng/mL. They were compared in terms of renal survival over the full follow-up period. Kaplan-Meier analysis demonstrated a significant difference in time-to-ESRD between the groups (Tarone-Ware test, $\chi^2 = 61.4$, $p < 0.001$). The median time to ESRD for Group 4 was 92 months, while it was not estimable for the other groups due to the small number of events. Five-year kidney survival was 84.8% (95% CI: 67.4–100%) for Group 1; 90.9% (95% CI: 75.4–100%) for Group 2; 85.7% (95% CI: 69.2–100%) for Group 3; and 57.1% (95% CI: 36.3–89.9%) for Group 4. Compared with Group 1, OR for ESRD development in Group 4 was 6.50 (95% CI: 1.19–52.38, $p = 0.044$), while no significant differences were found for Group 2 (OR = 0.59, $p = 0.684$) or Group 3 (OR = 1.08, $p = 0.941$). The Kaplan-Meier curve and OR plot are shown in Figure 2 A, B.

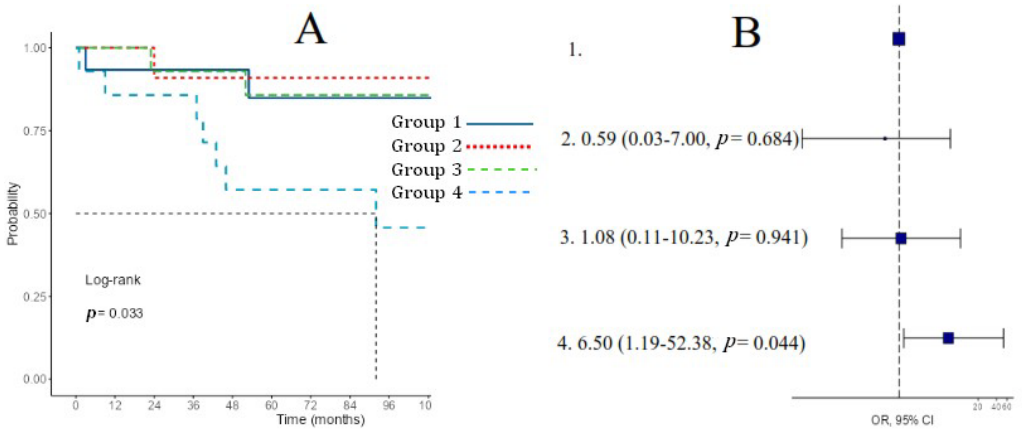

Fig. 2 – Serum neutrophil gelatinase-associated lipocalin (sNGAL) and development of end-stage renal disease: A) Kaplan-Meier curve (Tarone-Ware $p < 0.001$, Group 4 median – 92 months); B) OR plot. OR – odds ratio; CI – confidence interval.

***Note*: sNGAL concentrations (ng/mL) in Groups 1–4 were < 115.65, 115.66–154.71, 154.72–216.53, and > 216.53, respectively.**

Table 4

NGAL in relation to eGFR change during follow-up

Variables	Group 1	Group 2	*U* stat.	*p*-value	Effect size
n	12	37			
sNGAL	172.9 (69.2)	160.4 (102.2)	203	0.671	-0.086
uNGAL	15.2 (2.3)	13.3 (3.4)	141	0.061	-0.365
uNGAL/creatinine	22.9 (26.1)	17.0 (14.4)	137	0.049	-0.383
Age, years	39 (22.8)	53 (13.0)	157	0.133	0.293
eGFR	68 (30.8)	101 (34.0)	118	0.016	0.471
Total follow-up, months	110 (38.3)	113 (46.0)	200	0.609	0.101

NGAL – neutrophil gelatinase-associated lipocalin; eGFR – estimated glomerular filtration rate; *U* stat – *U* statistic; n – number of patients in the group; sNGAL – serum NGAL; uNGAL – urinary NGAL. Values are given as median (IQR). For units of measurement, see Table 1.

***Note*: Group 1 – an average annual eGFR increase or decline of < 1.5 mL/min/1.73m2; Group 2 – an average annual eGFR decline of > 1.5 mL/min/1.73m2.**

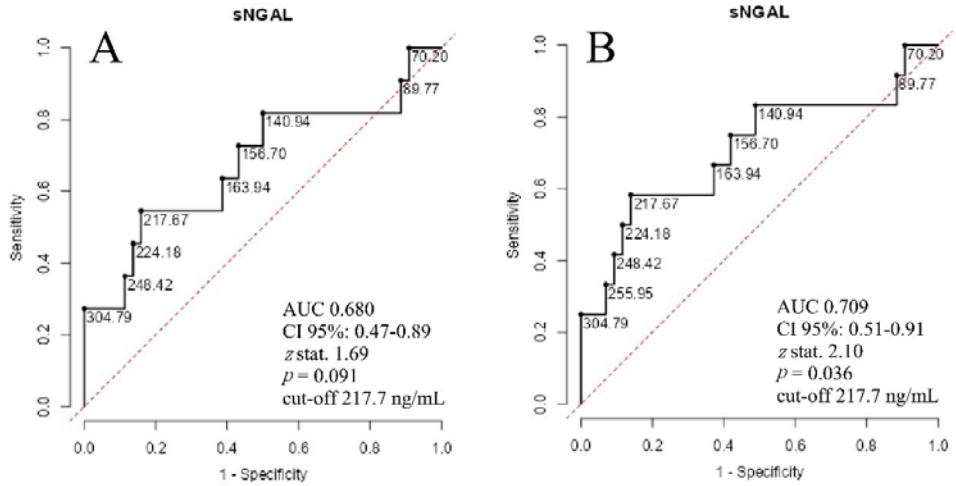

Fig. 3 – ROC curves for serum neutrophil gelatinase-associated lipocalin (sNGAL) in predicting renal survival: A) sNGAL for predicting end-stage renal disease (ESRD) development in a 5-year period; B) sNGAL for predicting ESRD development in the total follow-up period.
ROC – receiver operating characteristic; AUC – area under the curve; CI – confidence interval.

According to eGFR changes (average annual) during follow-up, 49 patients were divided into groups. Patients who were lost to follow-up, who died within the first year, or who lacked a final serum Cr were excluded from this analysis. Comparisons between the groups are presented in Table 4. Group 2 had a significantly lower baseline uNGAL/Cr ratio.

Logistic regression was used to assess the discriminatory ability of NGAL in predicting renal survivor. The ROC curves with *p*-values < 0.1 are shown in Figure 3A, B. The

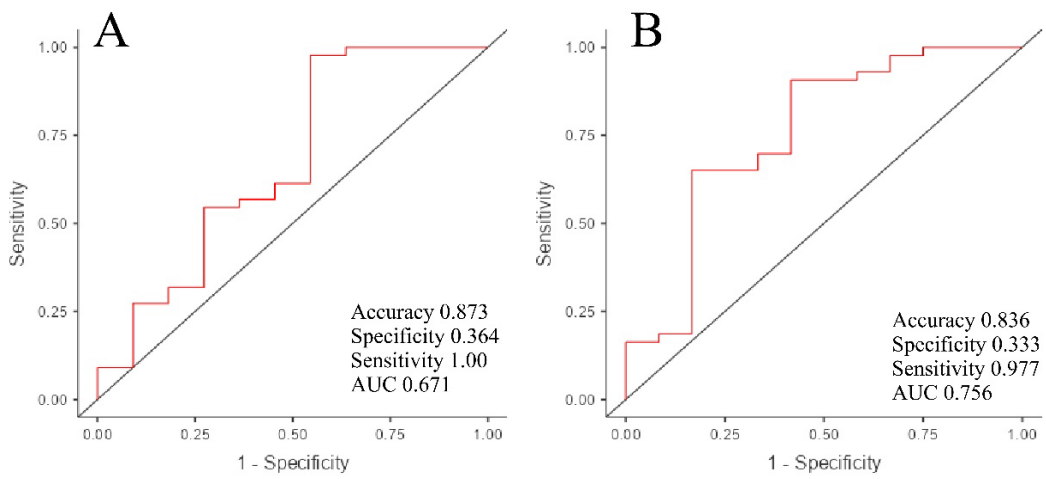

Fig. 4 – ROC curves for multivariate models in predicting renal survival: A) model for predicting end-stage renal disease (ESRD) after 5 years; B) model for predicting ESRD at the end of follow-up. ROC – receiver operating characteristic; AUC – area under the curve.

ROC curve for sNGAL indicated fair performance in identifying patients who would develop ESRD by the end of follow-up [area under the curve (AUC) = 0.709, 95% CI: 0.51–0.91, p = 0.036, cut-off = 217.7 ng/mL] (Figure 3B). Although the number of outcome events was limited, the analyses included a single predictor, which reduced the risk of overfitting.

Multivariate models with the discriminative ability of p-values < 0.1 for predicting renal survival, based on binomial logistic regression, are shown in Figure 4A, B. The model for predicting 5-year renal survival (Figure 4A), including baseline sNGAL, uNGAL, Cr, eGFR, diagnosis of proliferative vs. non-proliferative GN, and age, showed high sensitivity (1.0), but low specificity (0.364) and moderate discrimination (AUC = 0.671, p = 0.099). Supplementary Table 1 additionally shows the model for predicting ESRD development after 5 years.

The model for overall renal survival (Figure 4B), including baseline sNGAL, uNGAL, uNGAL/Cr, Cr, and eGFR, demonstrated good discriminative ability (AUC = 0.756), with high sensitivity (0.977), but low specificity (0.333) (p = 0.035). Supplementary Table 2 additionally shows the model for predicting overall ESRD development.

The results of both multivariate models should be interpreted with caution owing to the small number of patients who reached the study endpoint.

Discussion

Reference values for NGAL in healthy individuals are not clearly defined; the reported range for sNGAL is 7.8–109 ng/mL [10, 14, 15]. Previous studies have shown elevated levels of sNGAL and uNGAL in GN [4–6, 8, 11, 12, 16]. In our cohort, the median sNGAL (154.7 ng/mL) was consistent with these findings. In contrast, the median uNGAL (13.9 ng/mL) fell within the reported range for healthy individuals (0.34–20.41 ng/mL) [17, 18] and was lower than the 26.1 ng/mL reported in patients with PGN and lupus nephritis [12]. Our median uNGAL/Cr ratio (21.9 ng/mg) exceeded the value reported for the general population (4.2 ng/mg) [15].

No significant differences in uNGAL or sNGAL were observed among PGN subtypes in our study, consistent with Coppolino et al. [7] results. Values of uNGAL/Cr differed significantly between PGN subtypes in our cohort.

Both sNGAL and uNGAL correlated directly with baseline Cr and indirectly with eGFR, in line with previously reported data [5, 11]. However, some studies of glomerular diseases and diabetic nephropathy have not reported such correlations [7, 12, 16, 19]. Patients were followed for a median of 112 months. After 5 years, 18.33% of patients progressed to ESRD, increasing to 20% over the entire follow-up period, aligning with previously reported PGN rates (12.9–19.4% over 5 years; up to 60% over 10 years) [1]. The median time to ESRD was 38 months. Patients who progressed to ESRD had higher baseline sNGAL, compared to those who remained dialysis-independent, whereas Coppolino et al. [7] identified uNGAL as the stronger predictor. Kaplan-Meier analysis of renal survival demonstrated the lowest renal survival probability in patients with the highest sNGAL, with 5-year renal survival of 57.1% (vs. 84.8–90.9% in other groups). A fair discriminatory ability for predicting progression to ESRD was observed for sNGAL, with an optimal cut-off of 217.7 ng/mL. Elevated sNGAL in patients with CKD progression may reflect extra-tubular NGAL sources during active PGN. Renal mesangial cells produce NGAL in response to inflammation [8]. The cytokine environment in active PGN likely increases NGAL release into the circulation. NGAL influences cell motility and invasiveness in malignant cells [9], and functions as a chemoattractant [20]. Similarly, it may promote neutrophil recruitment to the kidney and modulate other inflammatory cells, thereby amplifying its own production. CKD progression in patients with elevated sNGAL may be related to its pro-fibrotic effects, which accelerate renal deterioration. Supporting this, Bonnard et al. [9] reported that a chemical NGAL inhibitor attenuated its pro-fibrotic and pro-inflammatory effects in renal and cardiac tissues.

In dialysis-independent patients, the uNGAL/Cr ratio was directly correlated with both absolute and annual eGFR change during the follow-up period, while uNGAL showed a borderline significant direct correlation with eGFR change. When comparing groups with different eGFR changes during follow-up, those with improved and/or stable eGFR had higher baseline uNGAL/Cr than those with eGFR decline. They also had higher uNGAL, but the difference did not reach significance. Data on the association between NGAL and longitudinal changes in renal function in PGN are limited. As mentioned, Copolino et al. [7] linked higher baseline uNGAL with CKD progression. Data on type 2 diabetes are inconsistent. Chou et al. [21] observed no association, whereas Żyłka et al. [19] found higher NGAL in patients with declining eGFR. Kielar et al. [22] linked higher uNGAL with eGFR decline after kidney transplantation. Our patients with improved and/or stable eGFR during follow-up had lower baseline eGFR compared with those with eGFR decline. When initiating treatment in PGN, therapy primarily aims to limit existing renal injury and to restore impaired kidney function, whereas in diabetes or after successful kidney transplantation, therapeutic strategies are largely aimed at preventing the onset and progression of renal damage. This difference limits the direct comparability of results across studies.

We observed a positive correlation between uNGAL and baseline proteinuria, consistent with findings from studies on glomerular diseases and lupus nephritis [4, 5, 11, 12, 16], but not previously reported in PGN [7]. This correlation can be explained by the increase in uNGAL during proteinuria. Filtration of sNGAL through the damaged GBM is increased [12]. Increased protein concentration in the tubules causes the cubilin-megalin transport mechanism overload, with reduced NGAL reabsorption [12, 16]. Tubular release of NGAL is increased due to the toxic effects of high cellular concentration of reabsorbed proteins, and decreased oncotic pressure and renal perfusion due to massive proteinuria [12]. Reduction in proteinuria during follow-up correlated negatively with both sNGAL and uNGAL. Those with greater reductions had higher baseline sNGAL and uNGAL. A positive correlation between the change in proteinuria and uNGAL change over time was reported before, but no comparison was made with baseline uNGAL [12].

Based on our findings, we can assume that abundant proteinuria leads to increased NGAL release in the kidneys, which may activate different mechanisms that contribute to proteinuria reduction. Other authors have arrived at a similar conclusion [5]. The association of high baseline uNGAL normalized by urine Cr with eGFR improvement may also suggest NGAL's protective role during active PGN. T-cell immunity plays an important role in PGN pathogenesis [23]. NGAL downregulates the Th17 cell effects, thereby preventing the development of severe forms of GN [6]. PGN is an inflammatory disease with intense tissue oxidative processes associated with GBM changes and podocyte injury leading to CKD progression [24–26]. NGAL can mitigate oxidative stress (OS), which is linked to CKD progression and mortality in CKD [14, 24, 25]. OS-induced NGAL release is believed to be a compensatory mechanism aimed at reducing the toxic OS effects [14, 25]. By binding to chemotactic proteins, NGAL clears inflamed tissue and regulates inflammation [14]. NGAL reduces apoptosis of endotoxemia-damaged tubular cells and protects against ischemia-reperfusion injury [27]. In addition to mitigating OS and inflammation and modulating T-cell-mediated immunity, NGAL may be involved in other mechanisms that prevent pathological changes in the kidneys, influencing a better PGN course.

It remains unclear which mechanisms would be triggered by NGAL in individual patients and which factors influence the occurrence or predominance of specific effects. Distinct biological roles of NGAL in serum and urine are possible, as in our study, sNGAL was more strongly associated with CKD progression, whereas uNGAL was associated with improvement in renal function. Several questions regarding the role of NGAL, particularly in PGN, remain unresolved, underscoring the need for further research to clarify the diagnostic and prognostic significance of NGAL in PGN.

Limitation of the study

This study has several limitations and strengths. It was conducted at a single center and included a relatively small number of patients. Because all PGN subtypes were analyzed collectively, the findings cannot be attributed to individual subtypes. The absence of a control group limited comparisons of baseline findings. The small number of patients reaching the predefined endpoint may have reduced statistical power. Furthermore, not all clinical, biochemical, and histological biomarkers known to influence renal survival and mortality in PGN were included in the analyses. Despite these limitations, the study has notable strengths. All patients had biopsy-confirmed PGN, were naïve to disease-specific treatment at enrollment, and were followed over a prolonged period. CKD due to causes other than PGN was an exclusion criterion.

Conclusion

Higher sNGAL was associated with the development of end-stage renal disease, possibly reflecting its pro-fibrotic effects. In contrast, elevated uNGAL/Cr was associated with eGFR improvement. Both NGALs correlated inversely with changes in proteinuria during follow-up. The observed correlations between NGAL levels and reductions in proteinuria, together with the relationship between the uNGAL/Cr ratio and improved or stable renal function, suggest that NGAL may activate adaptive processes associated with favorable outcomes. Measurement of both sNGAL and uNGAL at diagnosis may help identify high-risk patients with primary glomerulonephritis, who could benefit from intensified treatment. However, the small sample size, the limited number of patients reaching study endpoints, and the incomplete understanding of cellular mechanisms of NGAL underscore the need for further research to validate NGAL as a biomarker in primary glomerulonephritis.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Table 1

Model for predicting ESRD development after 5 years

Predictor	Estimate (95% CI: lower–upper)	SE	*Z*	*p*-value	OR (95% CI: lower–upper)
Intercept	6.031 (-6.945–19.006)	6.620	0.911	0.362	416.032 (9.64×10^{-4}–1.80×10^{8})
sNGAL	-0.003 (-0.017–0.009)	0.006	-0.580	0.562	0.996 (0.983–1.01)
uNGAL	0.095 (-0.128–0.317)	0.114	0.836	0.403	1.100 (0.880–1.37)
Age	-0.021 (-0.089–0.047)	0.035	-0.595	0.552	0.980 (0.915–1.05)
Creatinine baseline	-0.023 (-0.065–0.020)	0.022	-1.034	0.301	0.978 (0.937–1.02)
eGFR baseline	-0.023 (-0.096–0.050)	0.037	-0.612	0.540	0.977 (0.908–1.05)
Pr/nonpr GN	0.193 (-1.536–1.923)	0.882	0.219	0.827	1.213 (0.215–6.84)

ESRD – end-stage renal disease; CI – confidence interval; SE – standard error; OR – odds ratio; sNGAL – serum neutrophil gelatinase-associated lipocalin (NGAL); uNGAL – urinary NGAL; eGFR – estimated glomerular filtration rate; Pr/nonpr GN – proliferative or non-proliferative glomerulonephritis; AIC – Akaike information criterion; McF – McFadden's.
***Note*: This model corresponds to the results shown in Figure 4A. Model fit measures: deviance = 44.4, AIC = 58.4, R^2McF = 0.194; Overall model test: $\chi^2 = 10.7$, $df = 6$, p = 0.099. Model estimated using a sample size of 55 patients.**

Supplementary Table 2

Model for predicting overall ESRD development

Predictor	Estimate (95% CI: lower–upper)	SE	*Z*	*p*-value	OR (95% CI: lower–upper)
Intercept	6.085 (-2.603–14.772)	4.432	1.373	0.170	439.053 (0.074–2.60×10^{6})
sNGAL	-0.008 (-0.021–0.005)	0.007	-1.177	0.239	0.992 (0.980–1.01)
uNGAL	0.138 (-0.098–0.375)	0.121	1.147	0.251	1.149 (0.907–1.46)
uNGAL/creatinine	-0.024 (-0.082–0.033)	0.029	-0.839	0.402	0.976 (0.922–1.03)
Creatinine baseline	-0.022 (-0.056–0.012)	0.017	-1.284	0.199	0.978 (0.945–1.01)
eGFR baseline	-0.030 (-0.088–0.029)	0.030	-0.974	0.330	0.971 (0.916–1.03)

ESRD – end-stage renal disease; CI – confidence interval; SE – standard error; OR – odds ratio; sNGAL – serum neutrophil gelatinase-associated lipocalin (NGAL); uNGAL – urinary NGAL; eGFR – estimated glomerular filtration rate; AIC – Akaike information criterion; McF – McFadden's.
***Note*: This model corresponds to the results shown in Figure 4B. Model fit measures: deviance = 45.8, AIC = 57.8, R^2McF = 0.207; Overall model test: $\chi^2 = 12.0$, $df = 5$, p = 0.035. Model estimated using a sample size of 55 patients.**

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Comparative study between the efficacy of Isobar TTL and Isobar EVO systems for lumbar degenerative diseases and their effects on adjacent segment degeneration

Komparativna studija efikasnosti Isobar TTL i Isobar EVO sistema u lečenju lumbalnih degenerativnih bolesti i njihovog uticaja na degeneraciju susednih segmenata

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Abstract

Background/Aim. Lumbar degenerative diseases (LDD) are diseases that occur due to normal aging and degeneration of the lumbar spine. In addition to conservative therapies, surgical procedures become necessary to achieve satisfactory clinical outcomes. The aim of this study was to evaluate the effectiveness of the Isobar TTL and Isobar Evolution (EVO) systems of dynamic internal stabilization in the treatment of LDD and their effects on adjacent segment degeneration. **Methods.** This research involved 78 LDD patients treated with Isobar TTL or Isobar EVO dynamic internal stabilization devices. Patients were divided into two groups: TTL (n = 40) and EVO (n = 38). Visual analog scale (VAS) pain ratings, Oswestry Disability Index (ODI) scores, and modified MacNab criteria effectiveness evaluations were performed preoperatively, 1 and 3 months postoperatively, and at the final follow-up. Range of motion (ROM) and intervertebral space ratio (IVSR) were measured preoperatively and after the final follow-up. **Results.** In almost two years, 37 TTL and 33 EVO patients completed every examination. After surgery, VAS and ODI ratings in both groups improved significantly compared to preoperative levels ($p < 0.05$). The surgical effectiveness of the TTL and EVO groups was rated as excellent or good using the modified MacNab criteria (91.89% and 93.94%, respectively). Preoperative ROM and IVSR values did not differ between the groups ($p > 0.05$). At the final follow-up, the EVO group had a significantly higher ROM than the TTL group (4.46 ± 1.19° vs. 2.58 ± 0.71°; $p < 0.05$) and the ROM of adjacent segments in the TTL group was significantly higher than that of the EVO group (6.74 ± 1.55° vs. 5.83 ± 1.32°; $p < 0.05$). The IVSR of the operated and surrounding segments did not change substantially from preoperative to final follow-up ($p > 0.05$). Moreover, there was no significant difference in IVSRs between the two groups for the operated and neighboring segments at the final follow-up ($p > 0.05$). **Conclusion.** Isobar TTL and Isobar EVO dynamic stabilization systems demonstrated good clinical outcomes. The ability of Isobar EVO to inhibit neighboring segment motion may prevent degeneration.

Keywords:
lumbar vertebrae; orthopedic procedures; osteoarthritis, spine; spinal diseases; spinal fusion.

Apstrakt

Uvod/Cilj. Lumbalne degenerativne bolesti (*lumbar degenerative diseases* – LDD) su bolesti koje nastaju usled normalnog starenja i degeneracije lumbalne kičme. Pored konzervativnih terapija, hirurške procedure postaju neophodne da bi se postigli zadovoljavajući klinički ishodi. Cilj rada bio je da se proceni efikasnost *Isobar* TTL i *Isobar Evolution* (EVO) sistema dinamičke unutrašnje stabilizacije u lečenju LDD, kao i njihov uticaj na degeneraciju susednog segmenta. **Metode.** Istraživanje je obuhvatilo 78 obolelih od LDD, lečenih primenom sistema unutrašnje dinamičke

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stabilizacije *Isobar* TTL ili *Isobar* EVO. Bolesnici su bili podeljeni u dve grupe: TTL (n = 40) i EVO (n = 38). Procena bola pomoću skorova vizuelne analogne skale (VAS) i *Oswestry Disability Index* (ODI), kao i procena efikasnosti prema modifikovanim MacNab kriterijumima sprovedeni su preoperativno, 1 i 3 meseca postoperativno, kao i na završnom kontrolnom pregledu. Preoperativno i nakon poslednjeg kontrolnog pregleda mereni su obim pokreta (*range of motion* – ROM) i odnos intervertebralnog prostora (*intervertebral space ratio* – IVSR). **Rezultati.** Za skoro dve godine 37 bolesnika iz TTL grupe i 33 iz EVO grupe završila su sve kontrolne preglede. Nakon operacije, skorovi VAS i ODI u obe grupe značajno su se poboljšali u poređenju sa preoperativnim vrednostima ($p < 0,05$). Hirurška efikasnost u TTL i EVO grupama ocenjena je korišćenjem modifikovanih MacNab kriterijuma kao odlična ili dobra (91,89% i 93,94%, redom). Preoperativne vrednosti ROM i IVSR nisu se razlikovale između grupa ($p > 0,05$). Na poslednjem kontrolnom pregledu EVO grupa imala je značajno veći ROM nego TTL grupa (4,46 ± 1,19° vs. 2,58 ± 0,71°; $p < 0,05$), a ROM susednih segmenata u TTL grupi bio je značajno veći nego u EVO grupi (6,74 ± 1,55° vs. 5,83 ± 1,32°; $p < 0,05$). IVSR operisanih i okolnih segmenata nije se značajno promenio od preoperativnog do poslednjeg kontrolnog pregleda ($p > 0,05$). Takođe, nije bilo značajne razlike u IVSR između dve grupe za operisane i susedne segmente na poslednjem kontrolnom pregledu ($p > 0,05$). **Zaključak.** Sistemi dinamičke stabilizacije *Isobar* TTL i *Isobar* EVO pokazali su dobar klinički učinak. Sposobnost *Isobar* EVO sistema da ograniči pokretljivost susednih segmenata može doprineti sprečavanju njihove degeneracije.

Ključne reči:
pršljenovi, lumbalni; ortopedske procedure; kičma, osteoarthritis; kičma, bolesti; kičma, fuzija pršljenova.

Introduction

The term lumbar degenerative diseases (LDD) refers to disorders resulting from the natural aging and degeneration of the lumbar spine, which can produce symptoms such as lower back and leg discomfort, lower limb numbness, intermittent claudication, and bladder, bowel, or sexual dysfunction. After receiving conservative therapies, including oral prescription medication and epidural steroid injection, the majority of individuals with lumbar degenerative disorder get some degree of alleviation. Nevertheless, all individuals respond to conservative management, and surgical procedures become necessary for achieving satisfactory clinical outcomes [1, 2]. Currently, surgical lumbar posterior pedicle screw fixation includes two main types: rigid internal fixation and dynamic internal stabilization. A popular dynamic stabilization tool is the Scient'x Isobar TTL dynamic system. According to an earlier study, using the Isobar TTL system may improve the biomechanical conditions after surgery and prevent adjacent segment degeneration (ASD) [3]. However, the impact of the first-generation Isobar TTL system on preventing ASD remains to be fully validated [4, 5]. The Isobar Evolution (EVO) system is a new-generation dynamic internal stabilization system with improved three-dimensional flexibility, including increased Isobar rod rotation from ± 2° to ± 4.5° and a longitudinal displacement range of ± 0.2 mm to ± 0.8 mm [6]. These modifications increase the mobility of the operable segment, which lessens the adverse effects of compensatory mobility on the neighboring section. However, the efficacy of the Isobar EVO system and its protective effects on ASD remain to be further verified in clinical practice.

The aim of this study was to evaluate the efficacy of both Isobar TTL and Isobar EVO dynamic internal stabilization systems in the treatment of LDD and their effects on ASD.

Methods

A total of 78 patients suffering from single-segment LDD were operated on at the Department of Orthopaedics at Dongzhimen Hospital, Beijing University of Traditional Chinese Medicine, China, from June 2015 to April 2017. The operation was performed using either the Isobar TTL (n = 40) or Isobar EVO (n = 38) dynamic stabilization systems. The study was approved by the Ethics Committee of the Dongzhimen Hospital, Beijing University of Chinese Medicine (No. DZMEC-KY-2019-190, from December 6, 2019).

To evaluate the effectiveness of both systems and their protective impact on ASD, the clinical efficacy and radiological changes of a total of 70 individuals who had the necessary exams over two years were compared. From the original 78 patients, 70 were followed up for more than two years. For the TTL group, L2–3 (1 case), L4–5 (16 cases), and L5–S1 (20 cases) were the particular operated segments, whereas L4–5 (19 cases) and L5–S1 (14 cases) were the specific operated segments for the EVO group. In the EVO group, 28 patients had lumbar disc herniation, 2 had lumbar spinal stenosis, and 3 had lumbar degen-erative spondylolisthesis. In the TTL group, the corresponding numbers were 31, 4, and 2 patients, respectively.

Inclusion criteria were as follows: patients with a definitive diagnosis of single-segment LDD; lumbar spine radiological changes consistent with clinical symptoms and no significant instability (degenerative spondylolisthesis within II°); symptoms not effectively relieved after more than 6 months of conservative treatment; patients who gave their informed consent.

Exclusion criteria included: prior lumbar spine surgery; lumbar spondylolysis and lumbar degenerative spondylolisthesis ≥ II°; severe osteoporosis, ankylosing spondylitis, or other conditions unsuitable for surgery.

Operative procedures

Both patients from the EVO and TTL groups had identical surgical procedures. After successful anesthesia, the patient was placed in a prone position on a lumbar cushion with the abdomen suspended, followed by standard disinfection and sterile draping. The surgeon then incised the skin, subcutaneous tissue, and lumbar fascia layer by layer while assuming the median position of the waist. The spi-

nous processes of the index level and the lamina to the facet joint were exposed by dissecting the bilateral sacral spine muscles. Particular care was taken to preserve the facet joint capsule. Universal pedicle screws were inserted sequentially after identification of the index level using a C-arm X-ray system. The screws were fixed in place to prevent further adjustment after the direction of the screw tip was aligned as close as possible to the end plate of the vertebral body. The spinous process and part of the lamina at the stenotic level of the lumbar spine were then removed using a rongeur. To preserve the facet joint, the hypertrophied ligamentum flavum and hyperplastic epiphysis were carefully excised. The central spinal canal and nerve root canals were fully decompressed using lateral recess decompression. The herniated nucleus pulposus tissue was identified and removed. Unless the affected intervertebral disc was compressing the nerve root, it was not treated. Efforts were made to minimize disruption of the intervertebral space (IVS) at the operative segment. After complete decompression, the surgeon placed the dynamic rod in the appropriate position and tightened the locking bolts. Following adequate hemostasis and irrigation, an epidural drainage tube was placed, and the incision was closed layer by layer.

Clinical and radiologic evaluation

Clinical evaluation included assessment of the visual analog scale (VAS) and Oswestry Disability Index (ODI) scores preoperatively, at 1 and 3 months postoperatively, and at the final follow-up. At the final follow-up, surgical outcomes were also assessed using the modified MacNab criteria. Intraoperative blood loss, operation time, and postoperative complications, such as broken screws and rods, were also recorded.

Radiologic evaluation was performed before the procedure and at the final follow-up using lumbar spine X-rays obtained in the standing lateral and flexion-extension positions. Two radiological parameters were assessed: range of motion (ROM), which is the ratio of the mean heights of the trailing and leading edges of the IVS over the height of the anterior vertebral body (Figure 1a, b) [7], and the IVS ratio (IVSR), which is the ratio of the leading and trailing edges of the IVS over the height of the anterior vertebral body (Figure 1c) [8].

Statistical analysis

Statistical analysis was performed using SPSS version 19.0. The findings were shown as mean ± standard deviation. Quantifiable variables from preoperative and postoperative periods, as well as across the groups, were compared using paired samples *t*-tests or independent samples *t*-tests. Chi-square analysis was used to compare categorical data expressed as absolute counts. Statistical significance was set at $p < 0.05$.

Results

Patient's basic information

Initial operations were successfully performed on all patients. Among them, 33 patients in the EVO group and 37 in the TTL group completed all required evaluations over more than two years of follow-up. No complications, such as implant failure (e.g., screw or rod breakage) or adjacent segment instability or deformity, were observed at the final follow-up. Among the two groups, there were no appreciable variations in gender distribution, mean age, follow-up duration, surgery time, or bleeding volume ($p > 0.05$) (Table 1).

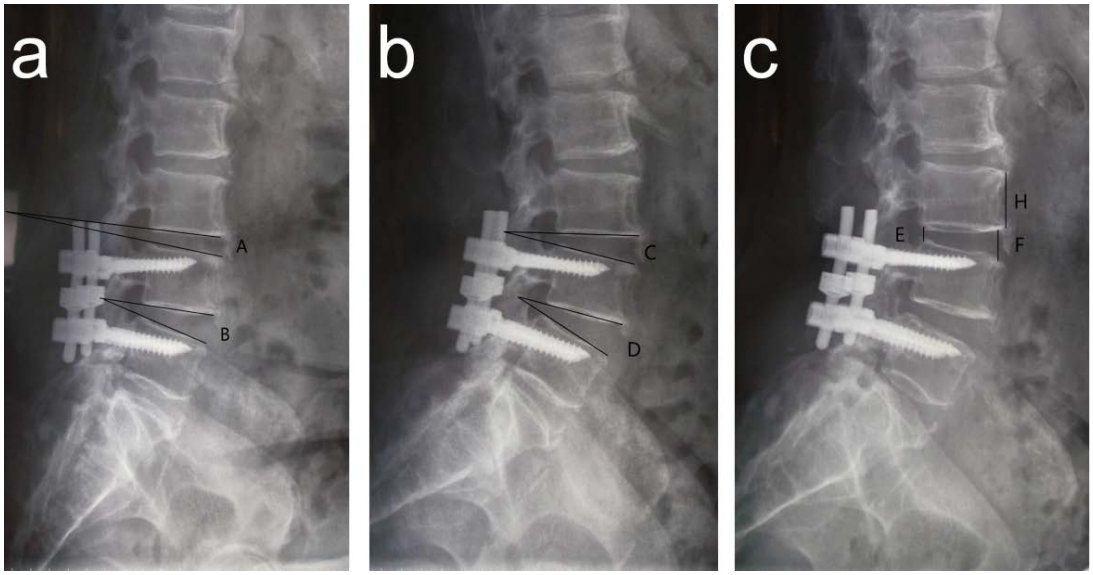

Fig. 1 – Lumbar range of motion (ROM) measurements: the anterior flexion angles (a, b) and the posterior extension angles (c). Dynamic stabilized segment ROM = D - B, adjacent upper segment ROM = C - A. Measurement of intervertebral space ratio (IVSR): F and E correspond to the height of the anterior and posterior intervertebral space, respectively, whereas H represents the height of the anterior upper vertebral body. IVSR = (E+F)/2H. ImageJ software was used in the study to measure angles and heights.

Table 1

Patient's basic information

Variable	Groups		*p*
	TTL (n = 37)	EVO (n = 33)	
Gender			
male	20	14	0.350
female	17	19	
Age, years	47.43 ± 9.63	49.76 ± 9.02	0.306
Surgery time, min.	168.65 ± 25.16	167.58 ± 19.57	0.844
Amount of bleeding, mL	179.19 ± 59.37	172.73 ± 68.57	0.674
Follow-up, months	38.27 ± 4.47	36.42 ± 3.27	0.055

n – number; min. – minutes.
All values are given as numbers or mean ± standard deviation.
***Note*: The chi-square test was used for gender comparison between the two groups; the independent samples *t*-test was used to compare other data between the two groups.**

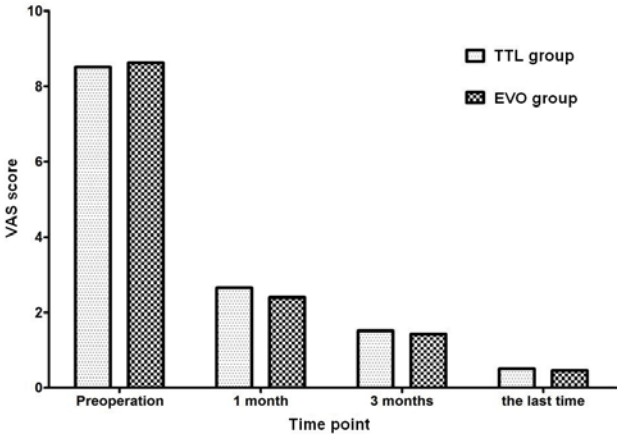

Fig. 2 – Different time points were used to calculate visual analog scale (VAS) values for the TTL and EVO groups.

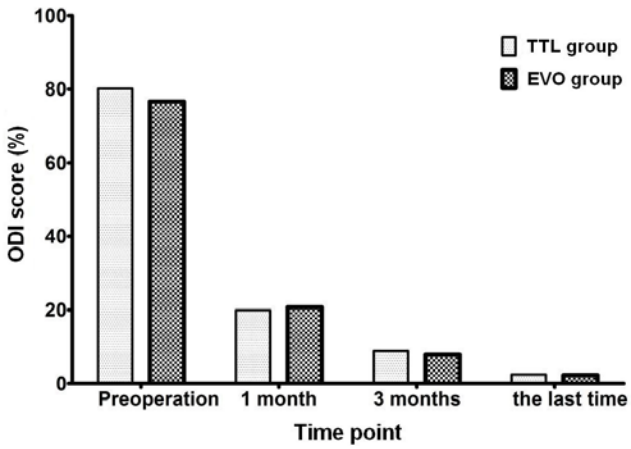

Fig. 3 – Oswestry Disability Index (ODI) scores of TTL and EVO groups at diverse time points.

Table 2

VAS and ODI score variations among the two groups at various time points

Variable	Groups		p_1	p_2	p_3
	TTL (n = 37)	EVO (n = 33)			
VAS (1–10)					
preoperative	8.08 ± 1.19 (5–10)	8.18 ± 1.04 (6–10)	0.709		
1 month postoperative	2.65 ± 1.23 (0–5)	2.39 ± 1.27 (0–5)	0.398	< 0.001	< 0.001
3 months postoperative	1.46 ± 1.32 (0–5)	1.48 ± 1.25 (0–4)	0.935	< 0.001	< 0.001
final follow-up	0.49 ± 0.84 (0–3)	0.48 ± 0.76 (0–3)	0.993	< 0.001	< 0.001
ODI (0–100)					
preoperative	79.43 ± 12.30 (46–98)	77.21 ± 20.95 (37.78–100)	0.586		
1 month postoperative	19.78 ± 5.75 (8.89–33.33)	20.99 ± 6.94 (11.11–40)	0.429	< 0.001	< 0.001
3 months postoperative	8.57 ± 3.98 (0–17.78)	8.17 ± 5.73 (0–22.22)	0.733	< 0.001	< 0.001
final follow-up	2.32 ± 3.18 (0–11.11)	2.44 ± 3.79 (0–15.56)	0.887	< 0.001	< 0.001

VAS – visual analog scale; ODI – Oswestry Disability Index; n – number.
All values are given as mean ± standard deviation (range).
***Note*: p_1 is a comparison between the TTL group and EVO group at the same time, using an independent samples *t*-test; p_2 is compared with preoperative in the TTL group, using a paired samples *t*-test; p_3 is correlated with preoperative in the EVO group, using a paired samples *t*-test.**

Changes in the visual analog scale score and Oswestry Disability Index score in patients

The VAS and ODI ratings in both groups significantly improved postoperatively compared to preoperative levels ($p < 0.05$) (Figures 2 and 3). Throughout the whole trial, there were no discernible differences between the two groups at any time intervals (preoperatively, 1 and 3 months postoperatively, and at the final follow-up) ($p > 0.05$) (Table 2).

Evaluation of the efficacy of surgery using modified MacNab measures

At the most recent follow-up, the surgical effectiveness of the TTL and EVO groups was judged as outstanding or good using the modified MacNab criteria (91.89% and 93.94%, respectively). There was no discernible difference between the two groups ($p = 0.933$) (Table 3).

Radiologic evaluation results

In both groups, the ROM of the surgically treated segments at the final follow-up was significantly lower than preoperative values (TTL: 6.82 ± 1.46°; EVO: 6.59 ± 1.85°). However, the ROM of the EVO group was substantially greater than that of the TTL group (4.46 ± 1.19° vs. 2.58 ± 0.71°) ($p < 0.05$). In both groups, the ROM of adjacent segments at the final follow-up was significantly higher than the preoperative values (TTL: 4.98 ± 1.12°; EVO: 4.87 ± 1.37°). Additionally, the TTL group exhibited a significantly greater ROM of adjacent segments (6.74 ± 1.55°) compared with the EVO group (5.83 ± 1.32°) ($p < 0.05$). There were no statistically significant intragroup changes in IVSR at either the operated or adjacent levels between the preoperative assessment and the final follow-up ($p > 0.05$). No significant differences were observed between the groups (Table 4).

Discussion

The safety and efficacy of fusion surgery, especially for spinal surgery, have been shown in several clinical investigations, where fusion has become a major surgical treatment option. However, it has also been well recognized that the subsequent increase of the stress load after fusion surgery at the adjacent segments may lead to an increased risk of ASD [9–13]. In a follow-up research, Liu et al. [14] discovered that the incidence of ASD following lumbar non-flexible fusion was 13.6%. A separate study of 101 patients with posterior lumbar interbody fusion surgery showed that ASD mainly occurred in the upper adjacent segments [15]. In the attempt to avoid an increase of biomechanical stress at the adjacent segments and prevent ASD, multiple dynamic stabilization systems utilizing posterior pedicle screws, such as the Graf, Dynesys, Cosmic, Isobar TLL, CD Horizon Agile, NFlex, AXIENT, Accuflex rod, PEEK rod, Stabilimax NZ systems have been developed [16].

Table 3

Comparison of the modified MacNab's effectiveness in both groups

Variable	Groups	
	TTL (n = 37)	EVO (n = 33)
Excellent	28 (75.68)	26 (78.79)
Good	6 (16.22)	5 (15.15)
Fair	3 (8.11)	2 (6.06)
Poor	0 (0)	0 (0)
Excellent or good, %	91.89	93.94
χ^2	0.138	
p	0.933	

n – number.
All values are given as numbers (percentages).
***Note*: The chi-square test was used for data comparison between the two groups.**

Table 4

Comparisons of ROM and IVSR of the operated and adjacent segments between the TTL and EVO groups

Variable	Groups		p_1	p_2	p_3
	TTL (n = 37)	EVO (n = 33)			
Operated segment					
ROM, °					
preoperative	6.82 ± 1.46 (5.03–11.23)	6.59 ± 1.85 (2.94–10.28)	0.564		
last follow-up	2.58 ± 0.71 (1.25–4.25)	4.46 ± 1.19 (2.55–7.55)	0.000	0.000	0.000
IVSR, %					
preoperative	36.91 ± 6.06 (22.34–47.56)	37.40 ± 9.21 (19.95–53.63)	0.791		
last follow-up	36.74 ± 8.81 (20.83–58.33)	37.73 ± 7.91 (21.69–58.63)	0.624	0.841	0.653
Adjacent segment					
ROM, °					
preoperative	4.98 ± 1.12 (3.13–8.48)	4.87 ± 1.37 (2.19–7.85)	0.705		
last follow-up	6.74 ± 1.55 (4.17–11.47)	5.83 ± 1.32 (4.03–9.69)	0.011	0.000	0.000
IVSR, %					
preoperative	40.82 ± 6.77 (27.55–57.22)	41.58 ± 6.78 (28.45–55.84)	0.637		
last follow-up	39.76 ± 7.49 (25.28–56.51)	41.03 ± 6.95 (27.76–56.14)	0.465	0.054	0.322

ROM – range of motion; IVSR – intervertebral space ratio.
All values are given as mean ± standard deviation (range).
***Note*: p_1 is a comparison between the TTL group and EVO group at the same time, using an independent samples *t*-test; p_2 is correlated with preoperative in the TTL group, using a paired samples *t*-test; p_3 is compared with preoperative in the EVO group, using a paired samples *t*-test.**

The load transfer behavior of the operated segment appears to resemble the physiological process with micromotion pedicle screw systems more than with rigid fixation, thereby reducing the stress load on the pedicle screw. These systems have the potential to prevent degeneration of the adjacent segmental intervertebral disc and lumbar facet joint, as well as alleviate pseudoarthrosis, osteoporosis, and additional mechanical damage [17–20].

Despite the above advantages, new issues related to the application of dynamic stabilization have emerged. Twenty-two individuals with PEEK rod lumbar fusion participated in a 2-year follow-up study by Oikonomidis et al. [21] which found that implant failure occurred in 4 patients, and 3 patients developed ASD in the upper neck. According to research, the Dynesys system's ability to maintain mobility may increase the risk of internal fixation, and the ROM of the operated segment gradually decreased, with unexpected small joint fusion occurring during follow-up [22, 23]. According to Peng and Gao [24], the Dynesys dynamic stabilization device should be chosen over fusion surgery for lumbar degenerative illnesses, although it is too soon to draw that conclusion.

Previous reports suggested that the Isobar TTL system may have the potential to delay ASD, improve pain relief and quality of life in patients with LDD, and have excellent long-term clinical and radiological results [25].

However, as reported in a systematic review, the existing research evidence is insufficient to demonstrate that the Isobar semi-rigid system has better clinical efficacy compared to titanium rods [26]. The three-dimensional mobility of the Isobar rod is only ± 2°, which is significantly lower than the physiological mobility of the lumbar segments [27]. Therefore, it is not surprising that some patients treated with the Isobar TTL system still develop ASD. A study using magnetic resonance imaging (MRI) to identify ASD reported an incidence of more than 39% (14/37) among patients undergoing Isobar TTL treatment [4]. It should be noted that the high resolution of MRI images may have enhanced the sensitivity in the detection of disc degeneration and thus contributed to the higher reported rate of ASD in that study.

The Isobar EVO system is designed to protect adjacent segments while preventing the development of ASD by allowing greater motion at the operated segment, thereby more closely simulating normal biomechanical characteristics. A related study has shown the potential of the Isobar EVO system to maintain the mobility of operated segments and to prevent further degradation of adjacent segments [6].

Published clinical trials have shown that using the Isobar TTL dynamic stabilization device to treat lumbar disc herniation reduces pain successfully (VAS score), improves lumbar function (ODI and Japanese Orthopaedic Association score), and reduces inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-α levels in serum [27, 28]. Our current study also showed significant early improvements observed in VAS and ODI scores at 30 days postoperatively in both groups of patients. Moreover, the above scores decreased further during subsequent follow-up. The VAS and ODI scores, however, did not differ significantly between the TTL and EVO groups at 1 month, 3 months, or at the final follow-up, indicating that both dynamic fixation systems successfully reduce symptoms and enhance patients' day-to-day functioning and capacity for work for at least 2 years. Both methods yielded excellent clinical outcomes over the study period, as evidenced by high excellent/good evaluations based on the modified MacNab criteria for both groups at the final follow-up (91.89% for the TTL group and 93.94% for the EVO group). These recent findings suggest that the two systems performed similarly in clinical outcomes.

According to Qian et al. [7], the ROM of the operated segment was 3.46 ± 1.02° preoperatively and 2.25 ± 0.79° at 12 months postoperatively in patients treated with the Isobar TTL dynamic internal stabilization system ($p > 0.05$). According to these authors, the Isobar TTL system could successfully maintain the mobility of operational sections. In our investigation, the ROM of the adjacent segments increased, whereas the ROM of the operated segments decreased at the final follow-up in both groups. Although the ROM of the operated segments in the EVO group (4.46 ± 1.19°) was greater than that in the TTL group (2.58 ± 0.71°), the ROM of adjacent segments in the EVO group (5.83 ± 1.32°) was lower compared to that of the TTL group (6.74 ± 1.55°). These findings indicate that both systems can only partially retain mobility in the operated segments, and that the increase in mobility at adjacent segments cannot be completely avoided. However, the compensatory increase in mobility of the adjacent segments by the Isobar EVO system was less severe and may be beneficial in reducing the risk of ASD.

Chou et al. [12] compared the "topping-off" technique (dynamic stabilization or less rigid fixation) with firm fusion fixation. They found that the firm fusion was associated with higher rates of degeneration in the two adjacent segments detected by X-ray (52.6%), symptom occurrence (11.6%), and secondary surgery (8.1%). When supra-ASD was detected by X-ray in the hybrid fixation group, it occurred at a lower rate (10.5%) than in the firm fusion cohort (24.7%). Thus, the scientists concluded that "topping-off" technology might significantly reduce the incidence of ASD.

In a comparison of the Isobar TTL system as well as a firm fixation system, Gao et al. [29] discovered that the apparent diffusion coefficient value of the dynamic fixation category was considerably better than that of the firm fixation group. This finding suggests that the Isobar TTL dynamic fixation system may be able to successfully prevent or delay intervertebral disc degeneration. In another study, Zhou et al. [30] discovered no significant differences in the relative grey-scale values of contiguous intervertebral discs in the Isobar TTL dynamic stabilization segment before and after surgery (23.98 ± 8.86 and 22.22 ± 6.25, respectively; $p = 0.46$). The authors concluded that this system might prevent the progression of ASD. In this manuscript, the IVS height ratio values at the final follow-up for the operated and adjacent segments were not significantly different from preoperative values in both groups. This indicates that both techniques were successful in preserving the IVS heights of the operative segment and preventing ASD. No significant difference in the IVS height ratio for the operated adjacent segments was observed between the two groups at the final follow-up. Therefore,

whether the two systems may perform differently in preventing ASD in the long run remains to be assessed.

Limitations of the study

We found no implant-related complications, such as screw loosening, screw breakage, or rod fracture, in patients treated with either system. Since the follow-up time was relatively short, the higher degree of mobility associated with the Isobar EVO system may lead to increased demands for repair of screws and rods. Whether the screws and rods can withstand the long-term clinical test remains to be evaluated. In addition, the sample size in this study was relatively small, and individual variability may have influenced the results. Larger studies are needed to further validate the clinical effectiveness of the Isobar EVO system and its impact on adjacent segments. Despite using the IVSR to assess the prevalence of ASD, previous research has shown that vertebral height is negatively correlated with age and follow-up duration [31]. The reliability of the IVS height ratio as a marker to assess the degeneration of the intervertebral disc may be affected, even if it may not be a severe problem in this short-term investigation.

It has been confirmed in relevant studies that using MRI to evaluate the intervertebral disc height index and Pfirrmann grading of intervertebral disc degeneration is a preferable option [32, 33].

Conclusion

The clinical efficacy of the Isobar TTL and Isobar EVO dynamic internal stabilization systems was satisfactory in the short term. Both systems partially retained the mobility of the operated segment and maintained the height of the intervertebral space of both the operated and the adjacent segments. More importantly, the Isobar EVO system restored the mobility of the operated segment to a greater extent than the Isobar TTL system. Therefore, the Isobar EVO system may have the potential to further reduce the risk of adjacent segment degeneration.

Conflicts of interest

The authors declare no conflict of interest.

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Quality of life of women with polycystic ovary syndrome of reproductive age

Kvalitet života žena u reproduktivnom dobu koje imaju sindrom policističnih jajnika

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Abstract

Background/Aim. Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, and it affects their physical and mental health and their quality of life (QoL). The aim of this study was to assess the QoL of women with PCOS of reproductive age. **Methods.** The study included 100 women, aged 18 years or above, diagnosed with PCOS. The Short Form Health Survey-36 (SF-36) was used as the research instrument. Mann-Whitney *U* test, Kruskal-Wallis test, and Spearman's rank correlation coefficient were used to examine possible differences in QoL within the variables studied. **Results.** Women with PCOS living in rural areas had a significantly higher mean score in the vitality domain. A statistically significant, strongly positive correlation with the total QoL score was found for the Mental Component Summary (MCS) ($p < 0.001$) and Physical Component Summary (PCS) ($p < 0.001$) subscales. A statistically significant but weak negative correlation was found between self-rated health and the PCS ($p = 0.021$), the MCS ($p = 0.004$) and the total QoL score ($p = 0.002$), and age with the PCS ($p = 0.023$) and the total QoL score ($p = 0.032$). **Conclusion.** Women with PCOS in rural areas were more vital and had better QoL. Lower self-esteem regarding health is associated with poorer QoL, especially in the psychological domain. In women with manifest PCOS, early diagnosis and appropriate education can help alleviate certain symptoms and prevent serious complications.

Keywords:
health; polycystic ovary syndrome; quality of life; surveys and questionnaires; women.

Apstrakt

Uvod/Cilj. Sindrom policističnih jajnika (*polycystic ovary syndrome* – PCOS) je najčešći endokrini poremećaj žena u reproduktivnom dobu i utiče na njihovo fizičko i mentalno zdravlje i na kvalitet života (*quality of life* – QoL). Cilj rada bio je da se proceni QoL žena u reproduktivnom periodu koje imaju PCOS. **Metode.** Istraživanjem je obuhvaćeno 100 žena starijih od 18 godina, kojima je dijagnostikovan PCOS. Kao instrument istraživanja korišćen je upitnik *Short Form Health Survey-36* (SF-36). Za ispitivanje mogućih razlika u QoL u odnosu na ispitivane varijable, korišćeni su Mann-Whitney *U* test, Kruskal-Wallis test i Spearman-ov koeficijent korelacije. **Rezultati.** Žene koje imaju PCOS i žive u ruralnim sredinama imale su značajno viši prosečni rezultat u domenu vitalnosti. Statistički značajna, jaka pozitivna korelacija sa ukupnim rezultatom QoL utvrđena je za podskale *Mental Component Summary* (MCS) ($p < 0,001$) i *Physical Component Summary* (PCS) ($p < 0,001$). Utvrđena je statistički značajna, ali slaba negativna korelacija između samoprocene zdravlja i PCS ($p = 0,021$), MCS ($p = 0,004$) i ukupnog skora QoL ($p = 0,002$), kao i između životnog doba i PCS ($p = 0,023$) i ukupnog skora QoL ($p = 0,032$). **Zaključak.** Žene u ruralnim područjima koje imaju PCOS bile su vitalnije i imale su bolji QoL. Niže samopouzdanje u vezi sa zdravljem povezano je sa lošijim QoL, posebno u psihološkom domenu. Kod žena sa ispoljenim PCOS se, uz ranu dijagnozu i odgovarajuću edukaciju, mogu ublažiti pojedini simptomi i sprečiti teške komplikacije.

Ključne reči:
zdravlje; jajnik, policistični, sindrom; kvalitet života; ankete i upitnici; žene.

Introduction

Polycystic ovary syndrome (PCOS) is a significant public health problem with a prevalence of approximately 15–20% in women aged 15–49 years [1]. Due to its complexity, up to 70% of women worldwide remain undiagnosed [2]. In 2016, 403 cases of coded PCOS diagnoses *per* 100,000 women aged 15 to 49 years were recorded in

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Slovenia, which may suggest a substantial level of underdiagnosis in this population [3].

The pathophysiology of the disease is not yet fully understood, but it is thought to result from genetic, metabolic, and environmental factors (e.g., lifestyle, obesity) [1, 4]. According to the Rotterdam consensus, PCOS is defined by the presence of two or three of the following criteria: anovulation and/or oligoovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovarian morphology (≥ 12 follicles with a diameter of 2–9 mm and/or an ovarian volume > 10 cm^3) [5–7].

PCOS as a reproductive syndrome can develop over time into a metabolic syndrome characterized by insulin resistance independent of body mass index (BMI) [8], impaired glucose intolerance, dyslipidemia, and increased body weight [9]. This, in turn, can lead to the development of type 2 diabetes mellitus [10] and increase the risk of cardiovascular disease (atherosclerosis, hypertension, heart attack) [11], breast and endometrial cancer [12], and, in rare but severe cases, obstructive sleep apnea. However, this is not a common outcome [13]. The severity of PCOS symptoms often varies over the course of a woman's reproductive life and manifests differently at various stages of life [14]. PCOS, a significant cause of infertility, affects more than just physical health. It often leads to emotional stress, reduced quality of life (QoL), and body image issues. If the condition is not diagnosed in time, it can cause serious health problems [15].

QoL is one of the most important measures for patients with chronic diseases [16]. As disease duration increases, overall QoL declines, along with perceived health status and QoL across the physical, social, and environmental domains [17]. The World Health Organization defines QoL as a subjective assessment of an individual's perception of reality in relation to personal goals, viewed within the context of their culture and value system [18]. QoL is a broad concept, defined as the perception of health or a conscious cognitive evaluation of satisfaction with life [19]. It is a useful indicator of overall self-perception of health and physical and emotional functioning in any illness [20]. Health-related QoL (HRQoL) is a multidimensional concept that examines how health affects QoL [19]. It is defined as a person's perception of their own life in the context of their culture and beliefs, as well as their personal goals and concerns [21]. It captures information about people's physical and mental health status and the impact of their health status on their QoL [22].

As PCOS can develop into a lifelong/chronic health condition, it is important to assess the HRQoL of women with PCOS [23]. Women with PCOS often have a lower HRQoL, which may be due to symptoms that currently cause them problems or fear of possible future disorders [24]. The HRQoL of women of reproductive age is negatively influenced by reproductive history and menstrual status [25], as well as PCOS and infertility as separate factors [26], obesity and body image disturbance [27], hyperandrogenism [2], anxiety and depression [28], a deterioration in women's self-esteem and self-image [17], changes in sleep quality, body image, and mood disorders [29]. PCOS affects all domains of the Short Form (SF) Health Survey, with PCOS having the most negative impact on psychological domains such as emotions and vitality [30]. HRQoL is significantly reduced in adult women with the anovulatory phenotype of PCOS [19]. PCOS has a negative impact on HRQoL in women with PCOS [1].

All members of the interdisciplinary healthcare team, including physicians, nurses, pharmacists, and other healthcare support staff, need to understand the concept of QoL to effectively support patients in achieving their health goals and improving their QoL [31].

The aim of this study was to assess the QoL of women with PCOS of reproductive age.

Methods

This cross-sectional study was conducted between May and July 2023 in 100 women diagnosed with PCOS at reproductive age.

A self-report questionnaire, the 36-item SF (SF-36), was used as the research instrument. More holistic health care focuses on a biopsychosocial model that emphasizes the patient's well-being and QoL. HRQoL is a multidimensional concept that describes the physical, emotional, and social aspects of certain diseases. Patient-centered measures or patient-reported outcome measures capture information that comes directly from the patient [1]. These measures include patient satisfaction, community integration, and social participation from the patient's perspective. This patient perspective is particularly important in research and clinical practice, especially regarding their functioning and health. The SF-36 is an instrument that has the highest methodological quality for assessing HRQoL [32]. The SF-36 is used to understand the impact of PCOS and to assess the health status of individual patients, as well as to monitor and compare the burden of disease [20, 33].

The pre-validated SF-36 questionnaire is a standard tool for assessing various aspects of HRQoL during the past four weeks. Respondents considered the four weeks preceding the date of questionnaire completion. The SF-36 comprises eight domains: general health, physical functioning, role limitations due to physical health, role limitations due to emotional problems, bodily pain, social functioning, vitality (energy/fatigue), and emotional well-being. The scores for each domain range from 0–100, with higher scores indicating better health [1, 23, 26]. We divided the eight QoL domains into two summarizing subscales: Physical Component Summary (PCS) with physical functioning, role limitations due to physical health, body pain, and general health domains and Mental Component Summary (MCS) with vitality (energy/fatigue), social functioning, role limitations due to emotional problems, emotional well-being domains, as well as the SF-36 total score [34, 35].

The questionnaire consisted of two parts. The first part collected socio-demographic data (age, place of residence, employment status, and self-rated health), while the second part contained the validated SF-36 questionnaire translated into Slovenian. The Slovenian translation of the SF-36 is a reliable and valuable validated tool that uses the SF-36 domains to assess HRQoL. Reliability testing of the SF-36 domains

included internal consistency and test-retest reliability. The Cronbach alpha coefficient for all SF-36 domains was above 0.78, and the Cronbach alpha coefficient for the SF-36 total score was 0.93 [36]. In this study, the Cronbach alpha coefficient for all domains of the SF-36 was 0.840.

Sampling technique

The questionnaire was developed using the online survey tool Google Forms. As we included only women with PCOS in the survey, a link to an anonymous online questionnaire was distributed *via* social media and PCOS support groups using a snowball sampling approach. All participants were recruited *via* posts on social media supporting women with PCOS (Facebook PCOS Slovenia), where they received a direct link to the first introductory part of the online survey. Upon accessing the survey, participants received information about the study. They were informed that all entries were anonymous and voluntary. Participants could only continue with the survey after they had given their consent.

The simple random sampling was carried out using Microsoft Excel software, whereby the women were assigned using the random numbers function – RAND, and the first 100 were selected according to their value.

Ethical consent

The data was collected using an anonymous online questionnaire. The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (including its Tokyo revision) and the Code of Ethics for Nurses and Nursing Assistants in Slovenia. Informed consent was obtained from all study participants. Participation was voluntary. Absolute confidentiality was guaranteed throughout the study.

Statistical analysis

Categorical variables were presented as percentages, while continuous variables were presented as arithmetic means with standard deviations, 95% confidence intervals, medians, and ranges. The Mann-Whitney *U* test was used to compare the mean scores of SF domains between two groups (by place of residence and employment status). The Kruskal-Wallis test with Bonferroni correction was used to compare the mean scores of SF domains among three groups (age groups and self-rated health). Spearman correlation was used to assess relationships between SF domains. Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics, version 29.0 (IBM Corporation, Armonk, NY, USA).

Results

The present study included 100 women over the age of 18 years (mean age 25.19 ± 4.02, range 18–39) diagnosed with PCOS. Most of the respondents (66%) lived in rural areas, with female students forming the largest subgroup (52%). A total of 39% of respondents rated their health as satisfactory (Table 1).

Differences in the quality of life of women with polycystic ovary syndrome – influence of sociodemographic factors

In the SF-36, respondents achieved the lowest mean scores in the areas of role limitation/emotions (22.33), role limitation/physicality (41.50), and MCS (42.77). There were no significant differences in age, employment status, or the SF domains. In all domains of the SF-36, the mean score of respondents living in rural areas was slightly higher. However, the Mann-Whitney *U* test only revealed a statistically significant difference in vitality (energy/fatigue) depending on place of residence ($Z = -2.122$; $U = 831.500$; $p = 0.034$). Pairwise comparisons showed that respondents in rural areas had a significantly higher mean vitality score (54.90) than respondents in urban areas (41.96).

Respondents who rated their state of health as very good had higher scores in all SF domains. The Kruskal-Wallis test shows statistically significant differences in the domains of role limitation/physicality ($H = 33.030$;

Table 1
Socio-demographic characteristics of PCOS women

Variable	Values
Age, years	
18–24	48
25–29	37
≥ 30	15
Place of residence	
urban area	34
rural area	66
Employment status	
studying	52
active working	48
Self-rated health	
very good	26
satisfactory	39
poor	35

PCOS – polycystic ovary syndrome.
All values are given as percentages.

$p < 0.001$), role limitation/emotion ($H = 19.641$; $p < 0.001$), PCS ($H = 6.700$; $p = 0.037$), MCS ($H = 8.199$; $p = 0.017$), and the total QoL score ($H = 9.695$; $p = 0.008$) on the self-rated health (Table 2).

Pairwise comparisons showed that in the role limitation/physicality domain, respondents who rated their health as very good were statistically significantly different from those who rated it as poor ($p < 0.001$) and statistically significantly different from those who rated their health as satisfactory ($p = 0.003$); respondents who rated their health as satisfactory were also significantly different from those who rated their health as poor ($p = 0.002$). In the area of role limitation/emotion domain, respondents with a very good self-rated state of health differed significantly from those who rated their state of health as poor ($p < 0.001$) or satisfactory ($p = 0.004$), while no significant difference was found between the "satisfactory" and "poor" groups ($p = 0.080$). In the PCS, respondents with a very good self-rated health status differed significantly from those who rated their health status as poor ($p < 0.001$) or satisfactory ($p = 0.004$), while no significant difference was found between the "satisfactory" and "poor" groups ($p = 0.080$). In the MCS, respondents with a very good self-rated health status differed significantly from those who rated their health status as satisfactory ($p = 0.014$) or poor ($p = 0.009$), although no significant difference was found between the "satisfactory" and "poor" groups ($p = 0.805$). In the total QoL score, respondents who rated their state of health as very good differed significantly from those who rated it as satisfactory ($p = 0.022$) or poor ($p = 0.002$), while no significant difference was found between the "satisfactory" and "poor" groups ($p = 0.885$).

Correlation analysis of quality of life and sociodemographic characteristics

A statistically significant, strongly positive correlation was found between the total QoL score and the PCS ($p < 0.001$) and MCS ($p < 0.001$) subscales. In contrast, a statistically significant but weak negative correlation was found between the self-rated health status and the PCS ($p = 0.021$), MCS ($p = 0.004$), and the total QoL score ($p = 0.002$). Age also showed a weak negative correlation with both the PCS ($p = 0.023$) and the total QoL score ($p = 0.032$) (Table 3).

Discussion

Assessing the QoL of people with PCOS is necessary as it provides a broader insight into the life and well-being of the individual. The results of our study show that women with PCOS living in rural areas scored higher in the vitality SF domain, possibly due to a more active lifestyle in nature and lower stress levels. Our findings indicate that women with PCOS generally reported a satisfactory self-assessment of their health. However, lower mean scores were observed

Table 2

Differences in the SF-36 domain scores in PCOS women

SF domain	Mean ± SD	95% CI	Median	Rank	*p*-value
PCS	51.51 ± 18.97	47.74–55.27	55.31	98.75	0.037†
physical functioning	64.05 ± 33.50	57.40–70.70	70.00	100.00	n.s.
role limit/physical	41.50 ± 43.11	32.95–50.05	25.00	100.00	< 0.001†
bodily pain	51.58 ± 27.33	46.15–57.00	45.00	100.00	n.s.
general health	48.90 ± 22.37	44.46–53.34	45.00	100.00	n.s.
MCS	42.77 ± 16.18	39.56–45.98	42.23	91.67	0.017†
role limit/emotion	22.33 ± 36.72	15.05–29.62	15.00	100.00	< 0.001†
vitality (energy/fatigue)	44.80 ± 18.23	41.18–48.42	45.00	100.00	0.034*
emotional well-being	53.19 ± 19.18	49.38–57.00	52.00	100.00	n.s.
social functioning	50.75 ± 23.82	46.02–55.48	50.00	100.00	n.s.
QoL – total score (SF-36)	47.14 ± 16.45	43.87–50.40	46.16	95.21	0.008†

SF-36 – Short Form Health Survey-36; PCOS – polycystic ovary syndrome; SD – standard deviation; CI – confidence interval; PCS – Physical Component Summary; MCS – Mental Component Summary; QoL – quality of life; n.s. – non-significant.

***Note*: *residence difference, Mann-Whitney *U* test with a $p < 0.05$; †general health difference, Kruskal-Wallis test with a $p < 0.05$. For an explanation on how the MCS and PCS are derived from eight subscales of the SF-36, see the Methods section.**

Table 3

Correlation analysis of quality of life and selected sociodemographic characteristics

Parameter	PCS	MCS	QoL – total score
Age	-0.227*	-0.147	-0.215*
Place of residence	-0.196	-0.138	-0.184
Job status	-0.119	-0.107	-0.143
Self-rated health	-0.230*	-0.287**	-0.300**
PCS	1.000	0.732**	0.932**
MCS	0.732**	1.000	0.918**

PCS – Physical Component Summary; MCS – Mental Component Summary; QoL – quality of life.

***Note*: * correlation is significant at $p < 0.05$; ** correlation is significant at $p < 0.01$.**

in several domains of the SF-36, particularly in role limitation/emotion, role limitation/physical, and vitality. The lower mean MCS score compared to the PCS further suggests that the mental, rather than the physical, component of QoL was more affected in respondents. The mean total QoL score was 47.14, indicating a tendency towards poorer emotional functioning and poorer HRQoL. Similarly, PCOS was found to have the strongest negative impact on psychological HRQoL [1]. It was also found that women with PCOS had a significantly lower mean HRQoL score of 43.4, with the lowest scores in domains such as vitality, emotional health, social functioning, physical pain, and general health [37]. On the other hand, in Spain, the SF-12 scale was used in a cohort of women with PCOS, and it was found that all women with PCOS had significantly lower scores on the PSC. The QoL of women with PCOS is worse, as PCOS has a negative impact on physical and mental health, as well as social activities [17]. When comparing women with ovulatory or anovulatory PCOS to the control group of women without PCOS, women with anovulatory PCOS had statistically significantly lower scores in the domains of role limitation/physical, vitality, and role limitation/emotion, while women with ovulatory PCOS had lower scores in the domains of general health and mental health. The greater differences in HRQoL among women with anovulatory PCOS are likely due to oligoovulation and hyperandrogenism, which are associated with infertility and issues related to self-esteem or self-concept [21]. With an early diagnosis and appropriate information, those affected can prevent serious complications and minimize the disturbing symptoms associated with PCOS [37].

The increasing incidence of PCOS worldwide requires a thorough investigation of its epidemiological trends and socio-demographic correlates. In 2021, the global prevalence of PCOS was estimated at 65.77 million cases, with 576.05 thousand disability-adjusted life years (DALYs) attributed to the condition. This represents an increase of 87% compared to 1990. The increasing trend can be observed in regions with a medium socio-demographic index, and the 45–49 age group has the highest DALYs rate in this region [38]. In 2021, there were 2.3 million new cases of PCOS, with the highest rates in Italy, Japan, and New Zealand. The increase in the prevalence and burden of PCOS is likely due to multiple factors. It is partly attributable to improved diagnostic criteria and reporting, but may also reflect a genuine rise associated with genetic, epigenetic, and environmental factors, as well as differences in the sociodemographic index between countries and regions [39].

Women with PCOS had a significantly lower QoL compared to healthy controls. The PCOS women with higher education had better HRQoL scores in all eight domains of the SF-36, but without statistically significant differences; those over 30 years of age had the lowest mean scores in the domains of role limitations/emotional (25.92), role limitations/physical (25.0), and general health (28.24) [23]. Similarly, in our study, we found a significantly weak negative correlation between age and PCS and total QoL scores, suggesting that older respondents have poorer HRQoL.

For women with PCOS, their socioeconomic status is a risk factor for disease acceptance; living in an urban environment and time since diagnosis (1 to 5 years) were significantly associated with poorer acceptance of PCOS [17]. In the present study, we also found the influence of place of residence on QoL. Respondents who lived in the countryside had slightly higher mean scores in all QoL domains and a statistically significantly higher score for vitality (energy/fatigue), implying that they have less of a negative impact on QoL. This could indicate a less stressful life in the countryside, where appearance is less important, as well as a lifestyle with more physical activity and contact with nature. In contrast, the QoL of women with PCOS was not related to disease duration or comorbidities. However, a significant correlation was found with the discomfort caused by PCOS symptoms. Most women with PCOS rated their QoL as good or very good, and those with very bothersome PCOS symptoms reported lower QoL than those whose symptoms were not categorized as very bothersome. Women with lower QoL felt they were not in control of the disease, suffered from depression, and did not accept their physical appearance [40]. In our study, we found a significantly weak negative correlation between rated health status and PCS, MCS, and total QoL scores, which, as expected, means that the worse the perceived health status, the lower the HRQoL.

Women with PCOS and BMI > 25 had a statistically significant and more pronounced lower QoL compared to healthy women and normal-weight PCOS women. However, the SF-36 domains of social function and physical function were significantly more impaired in PCOS women with a BMI > 25 compared to normal-weight controls [41]. Similarly, women with PCOS with a BMI > 30 had a statistically significantly lower mean score in the domains of general health (32.55), physical function (61.56), and energy/fatigue (48.43) [23].

Angin et al. [26] found that infertility negatively affects QoL, with the lowest SF-36 scores observed in the infertile PCOS group compared to the fertile PCOS group and the infertile non-PCOS group. The lowest scores were in the mental (44.0) and physical (44.4) components [26]. Infertility in women with PCOS is associated with psychological distress, which affects their sexual satisfaction, self-esteem, and QoL. However, infertility and psychological distress largely depend on ethnic background, religious beliefs, and personal desire to have children [42]. In addition to obesity and hirsutism, bodily pain is the main disorder that limits the physical QoL of PCOS women [43]. PCOS women score significantly worse in the domains of physical functioning and bodily pain on the SF-36 compared to healthy controls [44].

The risk of depressive symptoms is 2.5 times higher in women with PCOS than in healthy women [45]. Compared to healthy women, women with PCOS had significantly lower scores in the SF-36 domains PCS (67.31) and MCS (52.74), and significantly higher scores for depressive, anxious, and hyperthymic symptoms [46]. In this study, respondents who self-rated their health as very good reported fewer physical and emotional limitations and had statistically significantly

higher mean scores for PCS, MCS, and total QoL. This suggests that health perception is an important factor in assessing the HRQoL of women with PCOS and emphasizes the need for a holistic approach to the treatment of PCOS patients, which includes not only the treatment of symptoms but also the psychosocial aspects of the disease.

Physical and psychological problems are often exacerbated by cultural and societal pressures, which underscores the need to destigmatize PCOS. Healthcare professionals should be aware of the impact of PCOS on reducing QoL [47]. Nurses have a positive impact on women by supporting them, educating them about the disease and symptom management, raising awareness of prevention, and promoting health through a healthy lifestyle [48]. In addition, they must address the psychological dimensions of the disease and, above all, empower women to actively participate in the management of their own health.

Physical and mental health are closely linked and together form an important part of QoL. A poorer self-rated state of health is closely linked to a lower QoL, especially in the area of mental health. Effective management of PCOS requires an interdisciplinary healthcare team, with the gynecologist taking a leading role. The nurse can make an important contribution to the health promotion of women with PCOS by raising awareness and actively encouraging a healthy lifestyle. Shereda et al. [49] suggested that biopsychosocial nursing intervention significantly improved body image, depression, anxiety, stress, and overall QoL in women with PCOS.

As a health educator, the nurse plays an important role in encouraging women, particularly in urban environments, to maintain a healthy lifestyle and weight through a balanced, nutritious diet; regular, health-enhancing physical activity in green spaces or indoors when air pollution is present; restorative sleep; and effective stress management techniques.

Limitations of the study

The present study has some limitations. The women self-assessed their QoL. The SF-36 does not include physical and emotional symptoms related to the menstrual cycle, hirsutism, and infertility, which are important in women with PCOS and may affect their QoL.

Conclusion

In this study, we found that women with polycystic ovary syndrome who live in rural areas are more vital and have a better quality of life. Poorer self-rated health status is significantly associated with lower quality of life, particularly in relation to the psychological component. The relationship between the physical and psychological components of health and perceived quality of life thus emphasizes the need for a holistic approach in the treatment of women with polycystic ovary syndrome. With an early diagnosis and appropriate education, serious complications and minimization of some symptoms associated with polycystic ovary syndrome in affected women can be prevented.

Conflict of interest

The author declares no conflict of interest.

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Treatment of splanchnic artery aneurysms – single center results and experience

Lečenje aneurizmi splanhničnih arterija – rezultati i iskustva jednog centra

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Abstract

Background/Aim. Visceral artery aneurysms (VAAs) are rare but potentially life-threatening conditions. With the increasing availability of diagnostic and therapeutic options, there is a growing need to determine the optimal treatment approach–endovascular (EV) vs. open surgical (OS) reconstruction. The aim of this study was to analyze treatment outcomes in patients with VAA at a single center and compare the efficacy of EV and OS approaches. **Methods.** The study included 27 OS (the OS group) or EV (the EV group) interventions for VAA, performed at our institution from January 2010 to November 2023, on 27 patients, 13 males and 14 females, with a mean age of 57 ± 13 years. Treatment decisions were reached by a multidisciplinary team of a vascular surgeon, an anesthesiologist, and an interventional radiologist. **Results.** Out of the 27 patients, 9 were treated in the emergency setting, with 6 of them having ruptured aneurysms. The most common was a splenic artery aneurysm, 50.0% of all VAAs. Thirteen patients underwent EV reconstruction, one patient underwent a hybrid approach, and 13 patients had OS reconstruction. Technical success was 24/27 or 88.9%. Eleven patients were treated by coil embolization, while two were treated with the implantation of a covered stent. In the EV group, mortality was nil. In 14 patients, OS treatment was performed with 9 VAA resections and arterial reconstructions (7 with Dacron graft, 1 with polytetrafluoroethylene graft, and 1 with autovenous graft), with 2 splenectomies and 3 aneurysm exclusions. Two patients died intraoperatively due to severe bleeding, and one after the procedure because of intestinal ischemic complications. Mean duration of hospitalization after OS or EV procedure was 7.43 and 4.92 days, respectively. **Conclusion.** Treating patients using the EV approach is safe, with less invasiveness and shorter hospital stays, suitable for elective and emergency cases when technically feasible. OS remains a reliable option at high-volume centers, particularly for complex cases unsuitable for EV approaches or in low-risk patients. Treatment decision should be guided by VAA characteristics (size, symptoms, location, morphology), patient comorbidities, and specific clinical context, such as prior abdominal surgeries.

Keywords:
aneurysm; arteries; endovascular procedures; serbia; treatment outcome; vascular surgical procedures.

Apstrakt

Uvod/Cilj. Aneurizme visceralnih arterija (*visceral artery aneurysms* – VAAs) su retka, ali po život potencijalno opasna stanja. Sa porastom dostupnih dijagnostičkih i terapijskih mogućnosti, raste potreba za određivanjem optimalnog terapijskog pristupa–endovaskularna (EV) rekonstrukcija vs. otvorena hirurška (*open surgery* – OS) rekonstrukcija. Cilj rada bio je da se analiziraju ishodi lečenja obolelih od VAA u jednom centru i uporedi efikasnost EV i OS pristupa. **Metode.** Istraživanjem je obuhvaćeno 27 OS (OS grupa) ili EV (EV grupa) intervencija za VAA, sprovedenih u našoj ustanovi od januara 2010. do novembra 2023. godine, kod 27 bolesnika, 13 muškog i 14 ženskog pola prosečne starosti 57 ± 13 godina. Odluke o lečenju donosio je multidisciplinarni tim, koji su činili vaskularni hirurg, anesteziolog i interventni radiolog. **Rezultati.** Od ukupno 27 bolesnika, 9 je zbrinuto kao hitni slučajevi, od kojih je 6 imalo rupturu aneurizme. Najčešća je bila aneurizma slezinske arterije, 50,0% svih VAAs. Trinaest bolesnika podvrgnuto je EV rekonstrukciji, hibridnom pristupu 1 bolesnik, a OS rekonstrukciji 13 bolesnika. Tehnički uspeh bio je 24/27 ili 88,9%. Embolizacijom spiralama lečeno je 11 bolesnika, dok su 2 bolesnika lečena ugradnjom pokrivenog stenta. U grupi bolesnika lečenih EV putem nije bilo smrtnih ishoda. Kod 14 bolesnika urađeno je OS hirurško lečenje sa 9 VAA resekcija i arterijskih rekonstrukcija (7 *Dacron* graftom, 1 politetrafluoroetilen graftom i 1 autovenskim graftom), uz 2 splenektomije i 3 isključenja aneurizme. Usled jakog krvarenja, 2 bolesnika su preminula tokom operacije, a jedan posle zahvata zbog crevnih ishemijskih komplikacija. Prosečno trajanje hospitalizacije posle OS ili EV procedure iznosilo je 7,43 i 4,92 dana, redom. **Zaključak.** Lečenje EV pristupom je bezbedno, sa manje invazivnosti i kraćim boravkom u bolnici i

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pogodno je za elektivne i hitne slučajeve, kada je to tehnički izvodljivo. Primena OS pristupa ostaje pouzdana mogućnost u centrima sa velikim brojem operacija, posebno za složene slučajeve koji nisu pogodni za EV pristup ili kod bolesnika sa niskim rizikom. Odluka o lečenju treba da bude vođena karakteristikama VAA (veličina, simptomi, lokacija, morfologija), komorbiditetima bolesnika i specifičnim kliničkim kontekstom, poput prethodnih abdominalnih operacija.

Ključne reči:
aneurizma; arterije; endovaskularne procedure; srbija; lečenje, ishod; hirurgija, vaskularna, procedure.

Introduction

Visceral artery aneurysms (VAAs) represent a rare yet significant medical concern, as approximately 22% of cases necessitate urgent treatment, with a mortality rate of 8.5% [1]. The first documented case dates back to a 60-year-old woman in France, in whom a splenic artery aneurysm (SAA) was identified at autopsy [2]. Surgical intervention for VAAs saw its initial success in the early 20th century with the treatment of a hepatic aneurysm [3]. Over the past two decades, two major advancements have revolutionized the diagnosis and management of these aneurysms.

The advent of multi-detector computed tomography (MDCT) angiography has greatly facilitated diagnosis and treatment planning, revealing that VAAs may be more prevalent than previously believed [4, 5]. Prior to its widespread use, just over 3,000 aneurysms of splanchnic arteries had been documented in the literature. Additionally, the introduction of endovascular (EV) procedures has significantly decreased treatment risks, particularly benefiting elderly and high-risk patients, as well as those with surgically challenging aneurysm locations [6, 7].

The aim of this study was to analyze treatment outcomes in patients with VAAs treated at our center, provide a brief overview of clinical presentations, and summarize relevant literature to contextualize our findings and compare open surgery (OS) with EV repair.

Methods

From January 2010 to November 2023, a total of 27 OS (OS group) or EV (EV group) interventions for VAAs were performed at our institution in 27 patients, of whom 14 were female, with a mean age of 57 ± 13 years. The diagnostic method applied to all patients was MDCT angiography. Clinical management of the patients was investigated in terms of surgical therapy and interventional treatment. The treatment method was determined based on previously performed diagnostic evaluation, risk assessment, and the patient's clinical signs and symptoms.

The multidisciplinary team considered several factors when choosing between the EV and OS approach. Aneurysm diameter, morphology, and location were key determinants. For instance, asymptomatic patients with SAAs larger than 2 cm, as well as symptomatic lesions, were typically treated. In contrast, coeliac, hepatic, or superior mesenteric artery (SMA) aneurysms were treated regardless of size due to their high risk of rupture. Saccular aneurysms with a narrow neck were more amenable to coil embolization, whereas fusiform aneurysms, wide-necked lesions, or those with complex branch anatomy frequently required open or hybrid repair. Patient factors such as age, cardiopulmonary status, connective tissue disorders, pregnancy, portal hypertension, and prior abdominal surgery were also taken into consideration. High-risk patients and those with hostile abdominal anatomy were preferentially EV-treated, while low-risk patients with suitable anatomy were offered OS approach.

Descriptive statistics were used to summarize continuous variables (mean ± standard deviation) and categorical data (counts and percentages). Given the small sample size, formal hypothesis testing was limited to exploratory comparisons using the Student's *t*-test or Fisher's exact test as appropriate. A *p*-value below 0.05 was considered indicative of statistical significance.

Results

Data on patient age, gender, presenting symptoms and signs, diagnostic modalities, risk factors, comorbidities, and recent surgeries are presented in Table 1.

Table 1

Patient characteristics

Variable (n = 27)	Values
Female gender	14 (51.9)
Body mass index, kg/m^2	25.64 ± 3.45
Smoking	10 (38.5)
Hypertension	19 (70.4)
Hyperlipidemia	9 (33.3)
Diabetes mellitus	1 (3.7)
Coronary artery disease	3 (11.1)
Prior stroke/transient ischemic attack	0 (0)
Pancreatitis	4 (14.8)
Malignant disease	2 (7.4)
Chronic obstructive pulmonary disease	2 (7.4)
Connective tissue disease	1 (3.7)
Pregnancies	1 (3.7)

n – number of patients.
Data are given as numbers (percentages) or mean ± standard deviation.

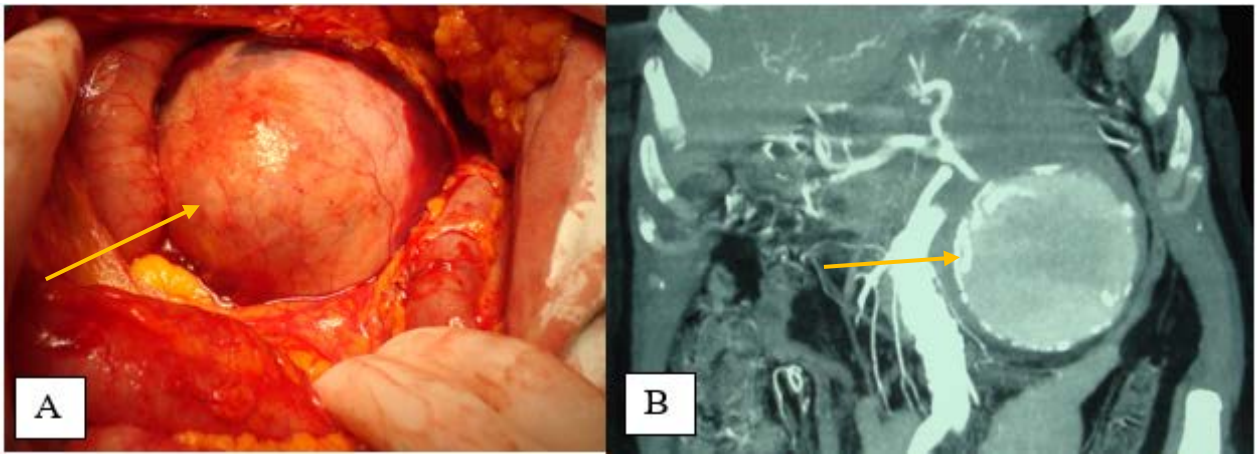

Fig. 1 – Splenic artery aneurysm: A) intraoperative look and B) multi-detector computed tomography angiography finding.

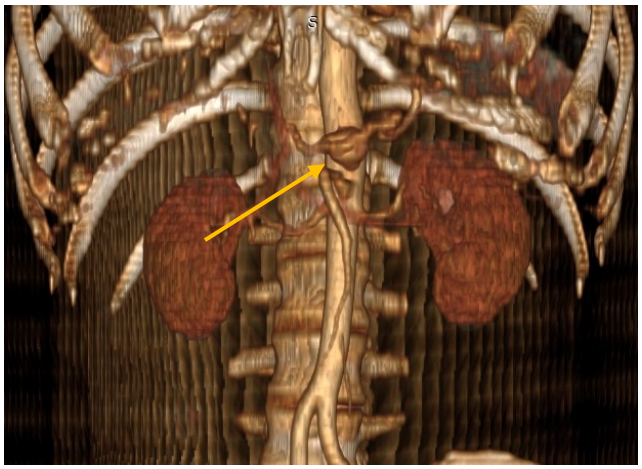

Fig. 2 – Three-dimensional multi-detector computed tomography angiography – aneurysmal enlargement of the coeliac trunk and its relationship to the main visceral branches.

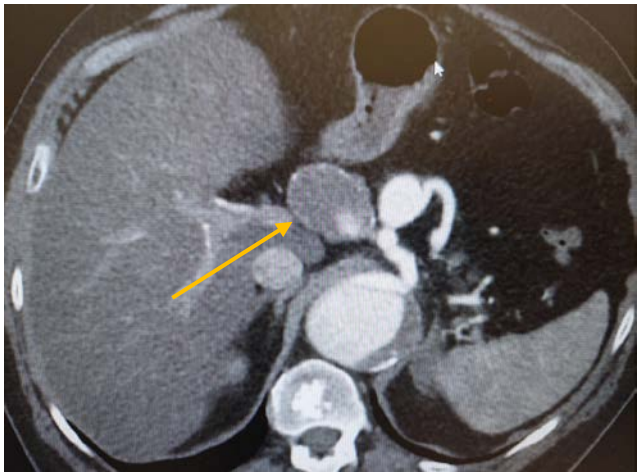

Fig. 3 – Aneurysm of common hepatic artery multi-detector computed tomography angiography – focal aneurysmal dilatation of the common hepatic artery, visualized as a contrast-filled vascular enlargement.

In the majority of cases, VAAs involved the splenic artery (Figure 1A, 1B) (n = 15), followed by the coeliac trunk (CoT) (Figure 2) (n = 5), the hepatic artery (Figure 3) (n = 4), and the SMA (Figure 4A, 4B) (n = 3). Besides the artery previously listed, VAAs involved pancreaticoduodenal artery (PDA), gastroduodenal artery, and distal medial colic artery, one case each (Table 2).

Of the 27 patients with 30 VAAs (Table 2), 13 were treated using the EV approach, while 13 underwent OS with a total success rate of 88.9%. In one case, the hybrid procedure

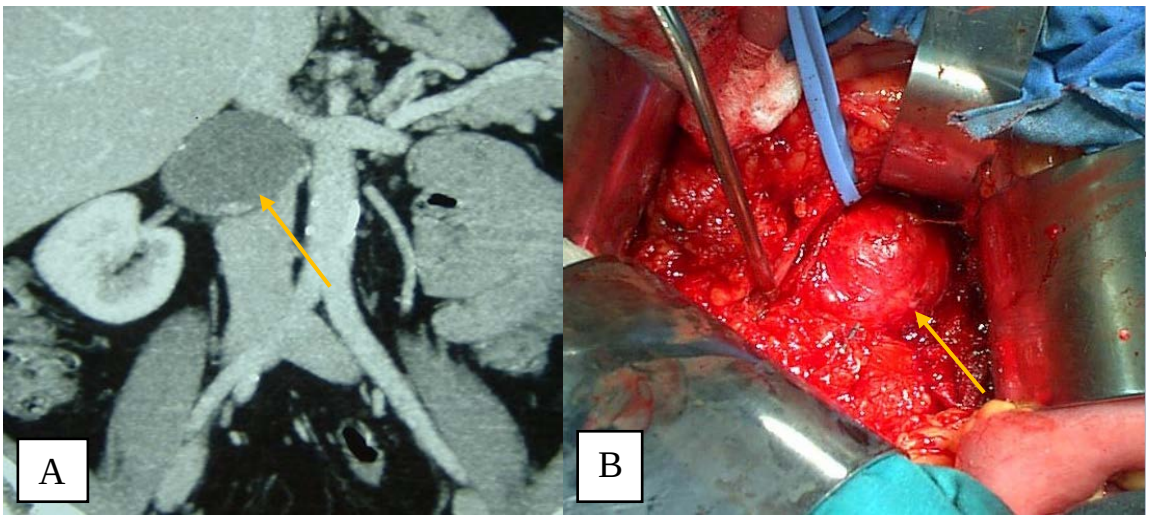

Fig. 4 – Aneurysm of superior mesenteric artery (SMA): A) multi-detector computed tomography angiography shows an aneurysmal dilatation of SMA, and B) intraoperative photograph of SMA after surgical exposure – the aneurysmal segment identified on preoperative imaging.

Table 2

Visceral artery aneurysms localization

Artery involved by an aneurysm (n = 30)	Values
Splenic artery	15 (50.0)
Coeliac trunk	5 (16.7)
Hepatic artery	4 (13.3)
Superior mesenteric artery	3 (10.0)
Pancreaticoduodenal artery	1 (3.3)
Gastroduodenal artery	1 (3.3)
Distal medial colic artery	1 (3.3)

n – number of aneurysms.
Data are given as numbers (percentages).
***Note*: The percentages in Table 1 were calculated based on the number of patients (n = 27), whereas in Table 2, the percentages were calculated based on the total number of aneurysms (n = 30). For this reason, one case shows slightly different percentages in Tables 1 and 2 (3.7% vs. 3.3%).**

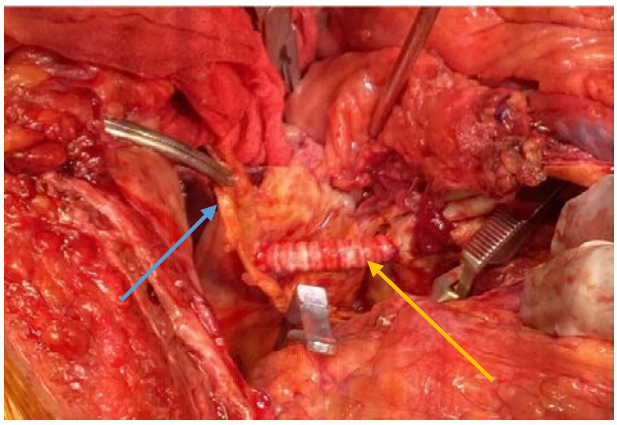

Fig. 5 – Resection of hepatic artery aneurysm (blue arrow) and Dacron graft interposition (yellow arrow).

was performed, which involved EV embolization of the aneurysm followed by surgical reconstruction. Eleven patients, of whom 10 had SAA and one had a PDA aneurysm, were treated by coil embolization, while 2 patients with SMA aneurysm were treated with covered stenting. In the EV group, mortality was nil, and there were no complications.

In 14 cases, surgical treatment was performed with 9 VAA resections and arterial reconstructions (Figure 5).

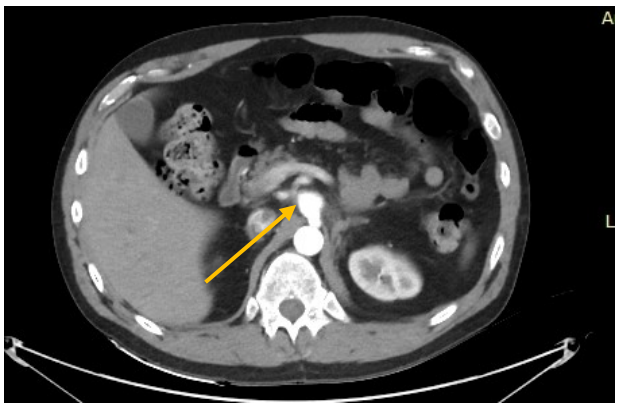

Fig. 6 – Multi-detector computed tomography angiography – an aneurysm of the coeliac trunk with surrounding contrast extravasation, indicating rupture.

Dacron graft was used in 7 cases, three times for CoT, twice for SAA, and twice for reconstruction of hepatic artery aneurysm (HAA). Polytetrafluoroethylene graft was used once in the treatment of an SMA aneurysm, and autovenous graft was also used once in the reconstruction of HAA. Splenectomy was performed twice, and aneurysm exclusion three times.

Out of 27 cases, emergency procedures were performed nine times, with 6 ruptured and 3 symptomatic aneurysms. SAA ruptured twice, and patients were treated with OS, aneurysm exclusion, and splenectomy with 100% successful rate. Two patients died during the operation due to the consequences of hemorrhagic shock, which resulted in a ruptured aneurysm of the CoT (Figure 6), and one after the procedure because of intestinal gangrene complications ($p = 0.077$). One of the patients who died intraoperatively was diagnosed with Ehlers-Danlos syndrome. Ruptures of the hepatic artery were successfully treated both times. EV intervention was performed once in an emergency case. Mean duration of hospitalization for OS treated patients was 7.43 days, and the mean duration after EV procedure was 4.92 days ($p = 0.063$).

Discussion

The distribution of splanchnic artery aneurysms is relatively consistent [8–15], with most (60%) occurring in the splenic artery, followed by the hepatic (20%), superior mesenteric (5%), and CoT (4%). Recent studies show similar trends, with SAA, coeliac, and SMA aneurysms comprising 55%, 27%, and 18% of cases, respectively [1]. About one-third are associated with aneurysms in other vascular territories such as the aorta or renal arteries [8].

In our cohort, the technical success rate (88.9%) was somewhat lower than the > 95% of rates reported in larger contemporary series, such as that of Batagini et al. [8]. Although mortality was nil in the EV group, three deaths occurred after OS repair. The relatively high proportion of emergency procedures (9/27 or 33%) and ruptured aneurysms (6 cases) likely reflects referral bias to our tertiary center. Distribution of aneurysm locations in our series–15 splenic, 5 coeliac, 4 hepatic, 3 superior mesenteric, and 3 other arteries–aligns broadly with epidemiological data. However, the proportion of CoT lesions was slightly higher than the 4–6% typically reported [12, 15]. We also observed one case of Ehlers-Danlos syndrome leading to fatal intraoperative rupture. This underscores that connective tissue disorders, while rare, should be considered in young patients with splanchnic aneurysms.

SAAs result from elastic fiber fragmentation and medial degeneration, associated with fibromuscular dysplasia [16, 17], splenomegaly, portal hypertension, and multiple pregnancies [1, 10, 18–25]. Chronic pancreatitis also plays a role [26]. HAAs, once mainly mycotic, now arise predominantly from atherosclerosis and medial degeneration [15, 27]. SMA aneurysms are increasingly linked to dissection [15, 28], while CoT aneurysms may be associated with Dunbar syndrome [29]. Pancreaticoduodenal and gastroduodenal aneurysms are often pancreatitis-related [30–32].

Rupture is the most severe complication, especially in SAAs during pregnancy (maternal mortality up to 70%, fetal mortality up to 95%) [17]. HAA and SMA aneurysm ruptures can cause intraperitoneal bleeding or intestinal ischemia [1–5, 33].

Diagnosis is usually incidental, confirmed by angiography or MDCT. Treatment decisions should be based on aneurysm location, size, and symptomatology. The new European Society for Vascular Surgery guidelines recommend considering EV or OS treatment for asymptomatic SAA, HAA, coeliac, and SMA aneurysms when their diameter reaches 30 mm, with surveillance for smaller aneurysms. PDA aneurysms warrant intervention at 15 mm, and pregnancy or symptomatic aneurysms warrant treatment regardless of size. The guidelines emphasize minimally invasive EV approaches whenever feasible, reserving OS repair for mycotic aneurysms or anatomy unsuitable for EV techniques, and recommend individualized imaging follow-up after repair. Overall, modern management underscores minimally invasive EV techniques, which have proven effective and safer alternatives to OS in suitable cases [34].

Recent data from multicenter series and systematic reviews emphasize a gradual shift toward EV management as

the first-line treatment for most splanchnic artery aneurysms, achieving technical success rates of 90–98% and low perioperative mortality (< 2%) in experienced centers [35–41]. These outcomes align closely with the results of the present series, where the predominance of EV therapy reflects a global trend toward minimally invasive strategies.

Compared to earlier OS cohorts, contemporary reports demonstrate significantly shorter hospital stays, lower transfusion requirements, and fewer postoperative complications, particularly in SAAs and HAAs [37, 39]. Nevertheless, OS repair remains justified in complex cases involving rupture, infection, or unsuitable anatomy for stent placement.

The higher share of emergency interventions and ruptured cases in this study may explain the modestly lower overall technical success rate compared to large reference series, where elective treatment predominates [36, 38]. Still, the complication and reintervention rates remain within the reported international range, supporting the safety and efficacy of the adopted treatment approach.

Overall, current evidence confirms that the management strategy used in this series is consistent with modern trends emphasizing individualized EV treatment, guided by lesion morphology, collateral circulation, and patient comorbidities.

This was a retrospective analysis from a single tertiary center with only 27 patients, which limits the statistical power and generalizability of our findings. The cohort was heterogeneous, encompassing aneurysms at multiple visceral locations and including both elective and emergency cases. Given that treatment decisions were individualized, selection bias may have influenced comparisons between EV and OS techniques. Long-term follow-up data on aneurysm patency, recurrence, need for reintervention, and survival were not available. Future multicenter prospective studies with standardized criteria and extended follow-up are needed to guide the management of splanchnic artery aneurysms better.

The management of splanchnic artery aneurysms involves a combination of imaging for diagnosis and a tailored approach to treatment, emphasizing EV techniques for their less invasive nature and effectiveness in reducing complications.

Conclusion

Splanchnic artery aneurysms are exceedingly rare, yet they carry significant medical importance due to their potential to manifest as acute surgical emergencies in a quarter of cases, often resulting in fatalities before diagnosis. Despite advancements in diagnostic imaging techniques such as multi-detector computed tomography and magnetic resonance imaging, their detection remains challenging due to nonspecific clinical symptoms and signs. Given the high mortality rate associated with rupture, surgical intervention is typically warranted even for asymptomatic splanchnic artery aneurysms. Endovascular procedures, such as embolization and stent graft placement, are preferred for high-risk patients or those with hostile abdominal anatomy due to their minimally invasive nature and shorter hospital stays. For elective management of visceral artery aneurysms, open surgery performed by experienced surgeons remains the standard of care, particularly in cases unsuitable or technically challenging for endovascular treatment in patients with low surgical risk. Treatment decisions should be guided by factors such as aneurysm size, symptoms, location, morphology, comorbidities, and previous abdominal surgeries.

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Pulmonary actinomycosis – a diagnostic dilemma

Aktinomikoza pluća – dijagnostička dilema

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Abstract

Introduction. Pulmonary actinomycosis is a chronic inflammatory infectious disease caused by anaerobic and/or microaerophilic bacteria of the genus *Actinomyces* spp. It causes non-specific symptoms in the patient and gives an atypical clinical and radiographic presentation. It is extremely rare and is characterized by the formation of abscesses and fistulas in the lungs or local fibrosis. In the differential diagnosis, diseases and pathological conditions from tuberculosis to neoplastic processes in the lungs must be considered. **Case report.** We present a 39-year-old patient with an infiltrative lesion in the apex of the right lung and non-specific symptoms. In this patient, actinomycosis was pathohistologically proven after surgical intervention. Within a period of just over a month, a multi-detector computed tomography of the chest and bronchoscopy with transbronchial biopsy and bronchial swab were performed twice. Initially, pulmonary actinomycosis was not suspected. After an atypical resection of the tumor mass in the apex of the right lung and histopathologically proven infection, the patient was treated with antibiotic therapy for 6 months. Further examination was carried out to prove a potential primary or secondary immunodeficiency. **Conclusion.** Patients with non-specific changes in the lung parenchyma should also be suspected of having actinomycosis, and after diagnosis, it is necessary to supplement the examination to confirm or exclude immunodeficiency.

Keywords:
actinomyces; actinomycosis; biopsy; bronchoscopy; diagnosis; multidetector computed tomography; thoracoscopy.

Apstrakt

Uvod. Aktinomikoza pluća je hronična zapaljenska infektivna bolest koju izaziva anaerobna i/ili mikroaerofilna bakterija iz roda *Actinomyces* spp. Izaziva nespecifične simptome kod bolesnika i daje atipičnu kliničku i radiografsku sliku. Veoma je retka i karakteriše je stvaranje apscesa i fistula u plućima, ili lokalna fibroza. U diferencijalnoj dijagnozi moraju se razmotriti bolesti i patološka stanja od tuberkuloze pluća do neoplastičnog procesa u plućima. **Prikaz bolesnika.** Predstavljamo 39-godišnjeg bolesnika sa infiltrativnom promenom u gornjem delu desnog plućnog krila i nespecifičnim simptomima. Kod ovog bolesnika, aktinomikoza je patohistološki dokazana posle hirurške intervencije. U periodu od nešto više od mesec dana, dva puta su urađene multidetektorska kompjuterizovana tomografija grudnog koša i bronhoskopija sa transbronhijalnom biopsijom i bronhijalnim brisom. U početku se nije sumnjalo na aktinomikozu pluća. Nakon atipične resekcije tumorske mase u gornjem delu desnog plućnog krila i histopatološki dokazane infekcije, bolesnik je lečen antibiotskom terapijom u trajanju od 6 meseci. Sprovedena su dalja ispitivanja da bi se potvrdila moguća primarna ili sekundarna imunodeficijencija. **Zaključak.** Kod bolesnika sa nespecifičnim promenama u plućnom parenhimu treba sumnjati i na aktinomikozu, a nakon dijagnoze potrebno je dopuniti ispitivanje kako bi se potvrdila ili isključila imunodeficijencija.

Ključne reči:
actinomyces; aktinomikoza; biopsija; bronhoskopija; dijagnoza; tomografija, kompjuterizovana, multidetektorska; torakoskopija.

Introduction

Actinomyces are opportunistic Gram-positive bacteria with a filamentous morphology, characterized by slow growth and the ability to cause infection. They are usually found in the oral cavity, in dental caries, and in the tonsils. Pulmonary actinomycosis (PA) is a chronic, purulent, granulomatous disease caused by the bacteria from the

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Actinomyces spp., of which *Actinomyces (A.) graevenitzii*, which is an anaerobic or microaerophilic bacterium, is the most causative agent [1, 2].

The largest number of infections occurs due to poor oral hygiene and inhalation of actinomycetes-containing secretions. Infections can also spread through the blood or through abdominal lesions. The most common infections are cervicofacial or abdominopelvic, while lung actinomycosis accounts for about 15% of all actinomycosis. The ratio of men to women is 3 : 1. The clinical and radiographic presentation of PA is non-specific and can lead to confusion, misdiagnosis, and wrong treatment. PA can resemble a tumor or tuberculosis in the lungs [3].

Factors associated with the development of PA include inadequate oral hygiene, periodontal inflammation, dental pathology, recent dental procedures, mucosal or thoracic trauma, aspiration events, states of impaired immunity, as well as previously existing actinomycosis at local or distant sites [4].

Two studies have shown that PA is accurately diagnosed in fewer than 4–7% of patients. Additionally, reports indicate that up to 25% of cases are initially misclassified as malignant disease [4, 5].

We present a patient whose actinomycosis in the lungs was confirmed after an atypical resection of the upper lobe of the right lung, and after non-specific findings on two bronchoscopies. After surgery, the treatment was continued with antibiotics.

Case report

A 39-year-old male patient presented to the emergency department with a cough lasting for the past 3 months and stabbing pain in the right scapular region. The pain worsened during coughing. He denied hemoptysis and reported occasional expectoration of greenish sputum. Vital parameters were stable: arterial blood pressure was 120/80 mmHg, pulse was 89 beats *per* min, and there were no changes on the electrocardiogram. Chest X-ray revealed an infiltrative lesion in the apex of the right lung. Laboratory tests showed the following: white blood cells 12.2 × 10^9/L [reference range (RR) 4.0–10.0 ×10^9/L] with a predominance of neutrophils, platelets 434 ×10^9/L (RR 150–400 ×10^9/L), C-reactive protein 41 mg/L (RR < 5 mg/L), and the rest was within the reference value limits. As there were no indications for emergency admission, the patient was discharged with cefixime and analgesic antipyretics as needed, and an outpatient contrast-enhanced multi-detector computed tomography (MDCT) of the chest was requested.

Chest MDCT showed an infiltrative lesion in the apex of the right lung, measuring 32 × 46 × 78 mm, with involvement of the visceral pleura, and surrounded by bullae and emphysema, along with a right paratracheal (4R) lymph node measuring 14 × 15 mm. An outpatient bronchoscopy with transbronchial biopsy (TBB) was performed 7 days after the initial presentation to the emergency center–endobronchial ultrasound radial probe with TBB, where the endoscopic findings were normal, and the histopathological (HP) findings were in favor of acute inflammation, with no signs of a specific inflammatory process and without any tumor infiltration.

As the patient's weakness, sweating, cough, and pain in the upper right hemithorax persisted, he returned to the emergency center 20 days after the initial examination. Vital parameters were stable again, and auscultatory findings were normal. The patient was given opioid analgesics and co-analgesics along with oral corticosteroids and gastroprotection therapy; a neoplastic process in the apex of the right lung was suspected. The day after the second examination at the emergency center, a repeated bronchoscopy was scheduled, and 7 days later, the patient was admitted to the hospital. Bronchoscopy again yielded non-specific HP findings–a mixed inflammatory infiltrate with a predominance of neutrophils and no evidence of malignant cells–from bronchial swabs and aspirates. HP analysis showed that the lung tissue was without neoplasm or specific inflammation. TBB was performed under X-ray control through the bronchus of the apical segment of the right lung, and bronchial swabs and aspirates were obtained for cytology, bacteriological analysis, acid-fast bacilli/Lowenstein testing.

Following the negative results of the above-mentioned tests, the patient was admitted for inpatient evaluation in a significantly improved general condition, with pain fully controlled by opioids. He was not receiving treatment for any chronic conditions, denied drug and food allergies, and reported no history of serious illnesses, injuries, or surgeries. He was in good general condition, self-motivated, physically active, and able to work. The patient reported undergoing dental prosthetic procedures on both jaws in 2015 (the upper jaw), and, in August 2022, a tooth root extraction in the lower jaw followed by placement of a dental bridge. He also reported a smoking history of approximately 20 pack-years.

During the hospital treatment, a second chest MDCT was performed, revealing a heterogeneous lesion in the apical segment of the right lung measuring 42 × 70 × 65 mm. The lesion appeared partly as consolidation and partly as an infiltrative lesion, surrounded by smaller inflammatory zones. High subpleural zones of hypodensity were present, possibly corresponding to zones of necrosis; some of them contained gas inclusions, for which it is not possible to say with certainty whether it was the formation of an abscess or zones of necrosis around subpleural bullae. Minimal right-sided pleural effusion was also observed. Right bronchopulmonary and paratracheal lymph nodes measuring up to 15 mm were noted (Figures 1–6).

Pulmonary function tests were performed. Spirometry showed a forced expiratory volume in one second (FEV1) of 3,330 mL or 86.3% (RR ≥ 80% of predicted) and a forced vital capacity (FVC) of 4,650 mL or 99.6% (RR ≥ 80% of predicted). The FEV1/FVC ratio was 71.66% (RR ≥ 70%). Maximal expiratory flow at 75% was 73.8% (RR ≥ 65% of predicted), maximal expiratory flow at 50% was 57.4% (RR ≥ 65% of predicted), and maximal expiratory flow at 25% was 47.3% (RR ≥ 60% of predicted). Diffusion capacity for carbon monoxide (DLCO) was 71.2% (RR 80–120% of

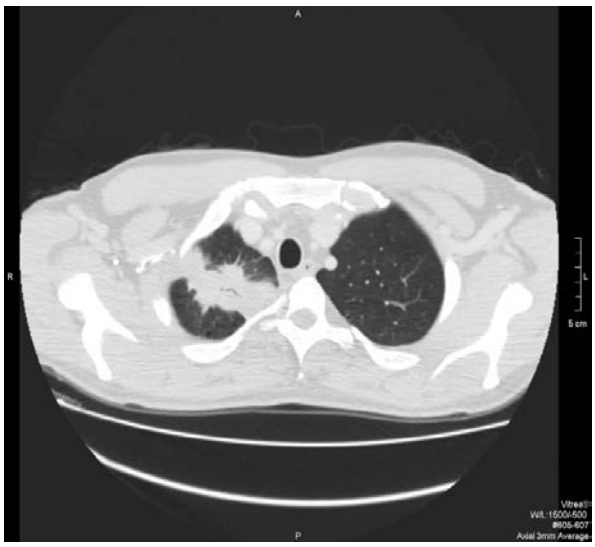

Fig. 1 – Chest multi-detector computed tomography: infiltrative/consolidative lesion in the apex of the right lung characterized as infiltrative (axial section).

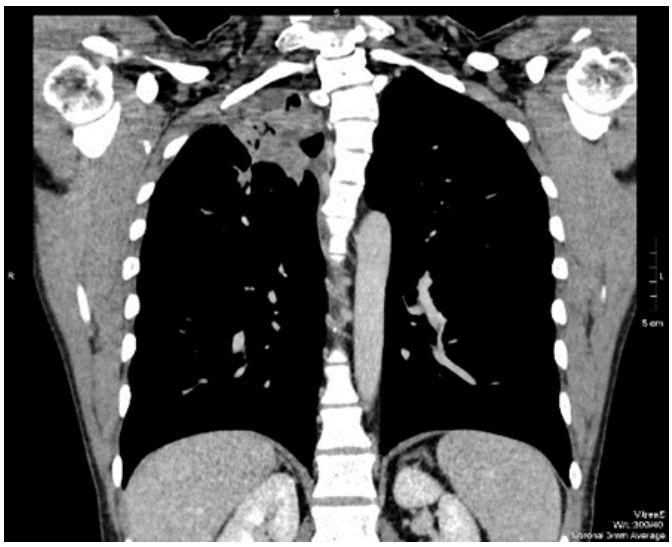

Fig. 2 – Chest multi-detector computed tomography: above lesion visible areas of necrosis (coronal section).

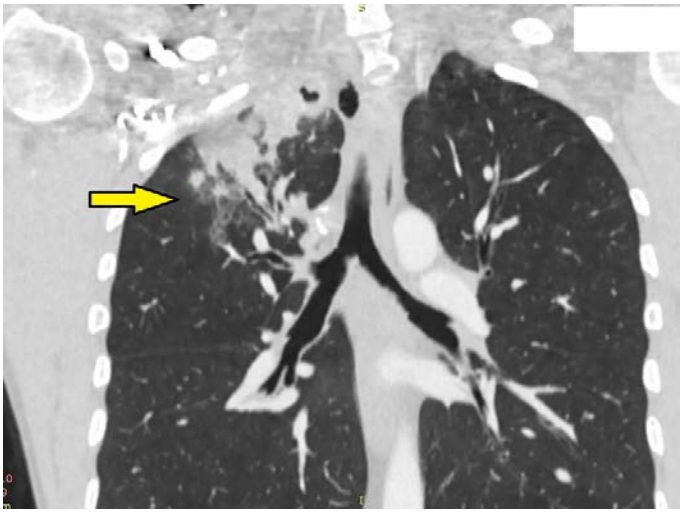

Fig. 3 – Chest multi-detector computed tomography: adjacent zones of patchy consolidation and pneumonitis.

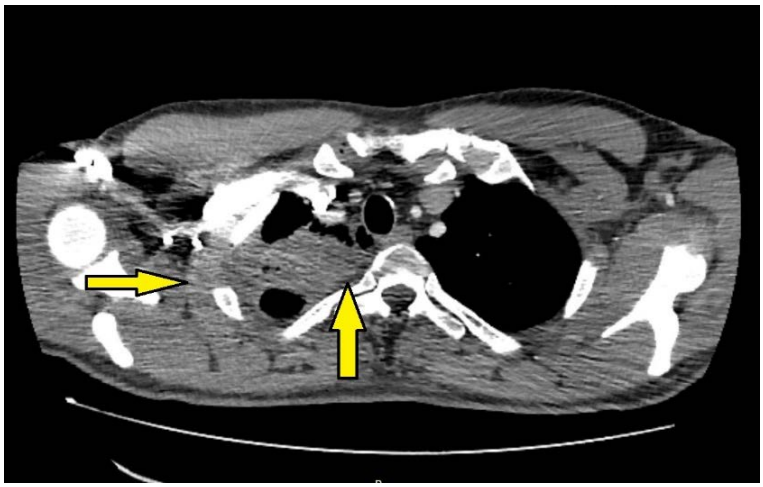

Fig. 4 – Chest multi detector computed tomography (axial section) demonstrating areas of demarcation between pulmonary parenchymal changes and the adjacent pleura (arrows).

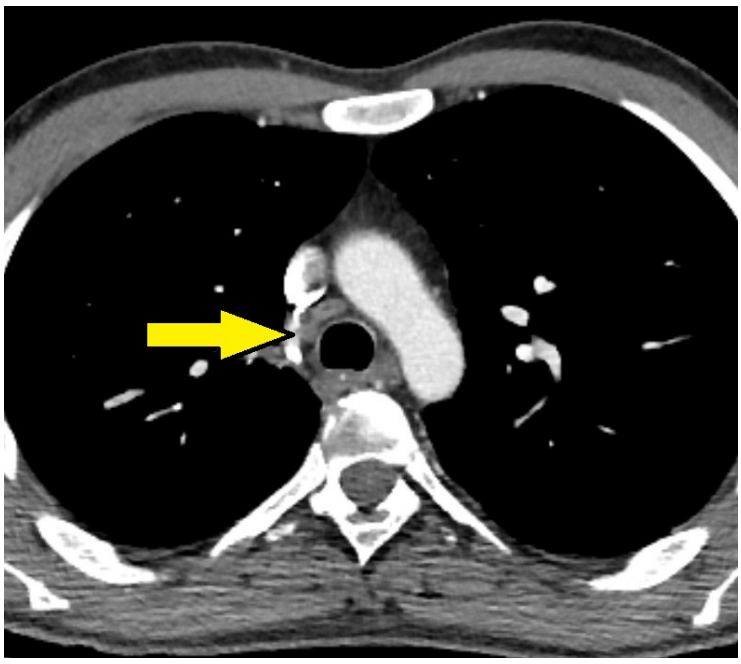

Fig. 5 – Chest multi-detector computed tomography: enlarged right lower paratracheal (station 4R) lymph node (axial section).

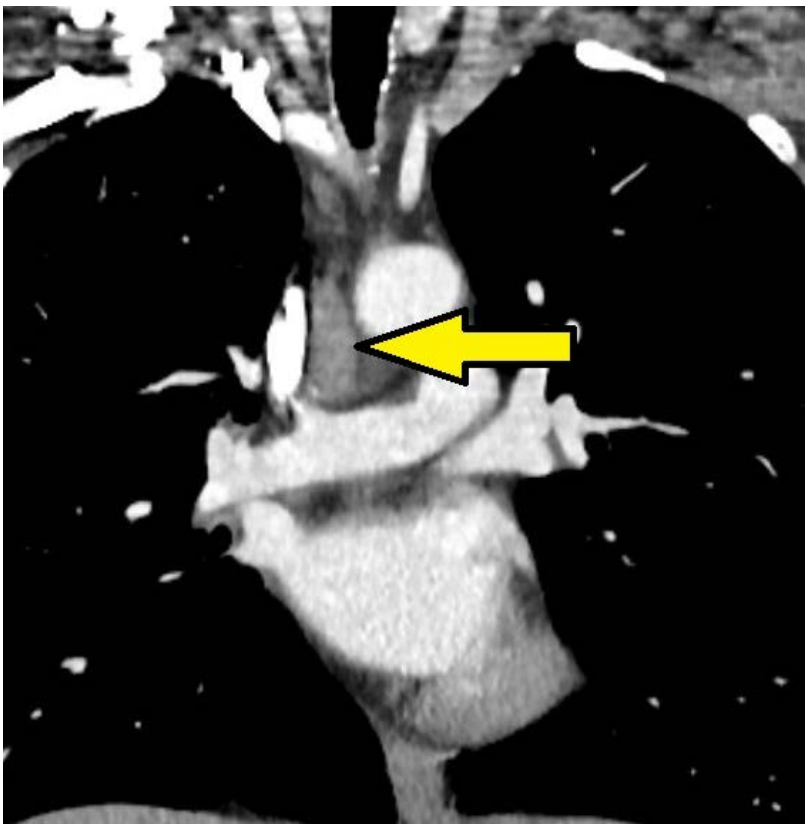

Fig. 6 – Chest multi-detector computed tomography: enlarged right lower paratracheal (station 4R) lymph node (coronal section).

predicted). Diffusing capacity divided by the alveolar volume (DLCO/VA) was 72.3% (RR 80–120% of predicted). Laboratory tests showed mild leukocytosis and slightly elevated inflammatory markers, while other parameters were within reference ranges.

During hospital treatment, the patient was treated with a parenteral antibiotic (ceftriaxone), and therapy was continued with tapentadol (sustained release). Throughout the hospital treatment, the patient was afebrile, and the pain syndrome was no longer present.

A thoracic surgeon was consulted, and the patient was prepared for a diagnostic and therapeutic thoracic surgical procedure due to the suspicion of a neoplastic process of the right lung.

A month after the initial examination in the emergency center, video-assisted thoracoscopy (VATS) and atypical resection of the upper lobe of the right lung were performed. Operative findings revealed that the apical segment of the upper lobe was attached to the mediastinal and costal pleura. The apical segment was almost entirely firm in consistency, more by type of consolidation. A biopsy was performed on the altered part of the upper lobe. The tissue was sent for *ex tempore* examination, which indicated a benign finding (inflammation). Athesiolysis of the upper lobe was performed with a sharp blunt preparation. Then, an atypical resection of the upper lobe with a change was performed with the help of endoscopic mechanical staplers.

The definitive HP finding was chronic bronchopneumonia in acute exacerbation with suppurative abscess formation and incomplete organization, pulmonary actinomycosis, perifocal cholesterol pneumonitis, fibrosis of the visceral pleura, and recent intraalveolar hemorrhage (Figures 7–11).

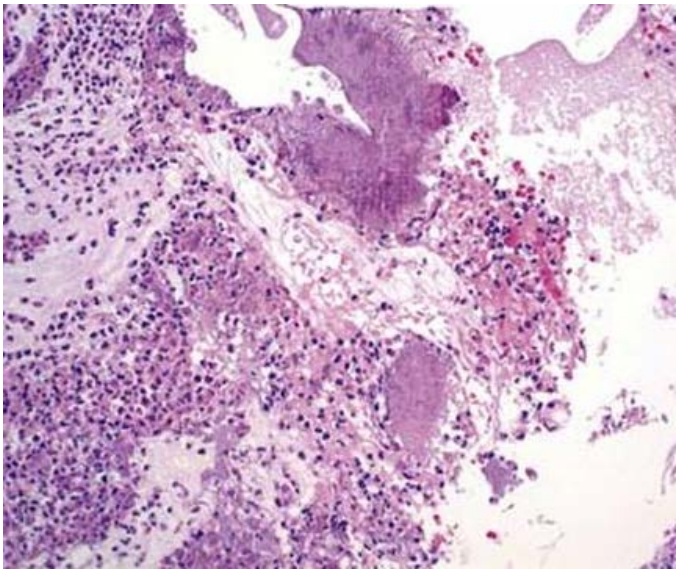

Fig. 7 – Histological examination of the sample lung parenchyma: inflammatory cellular lymphoplasmacytic infiltration and colonies of *Actinomyces* spp. surrounded by necrotic tissue and inflammatory cells (hematoxylin-eosin staining, ×10).

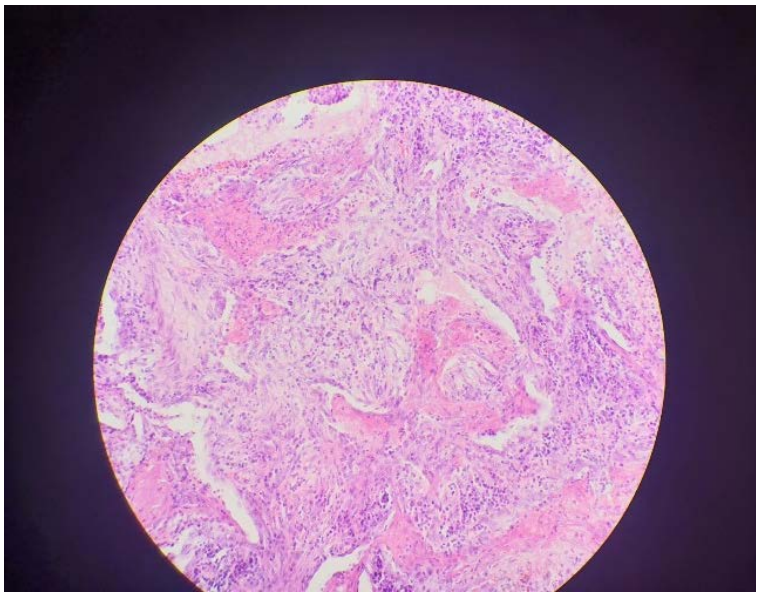

Fig. 8 – Masson bodies (hematoxylin-eosin staining, ×4).

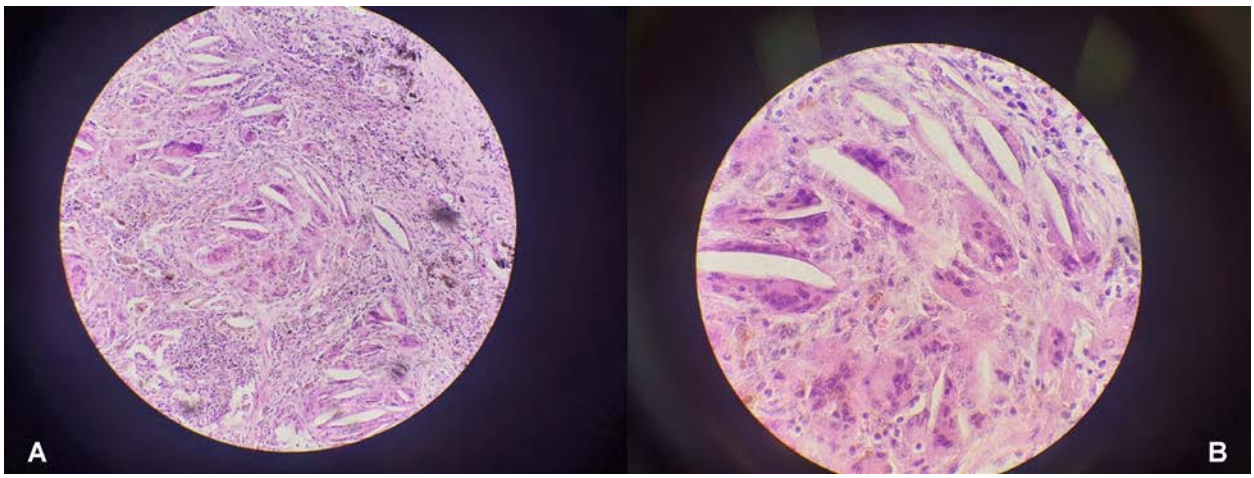

Fig. 9 – Cholesterol granulomas: hematoxylin-eosin staining magnification, ×10 (A) and ×20 (B).

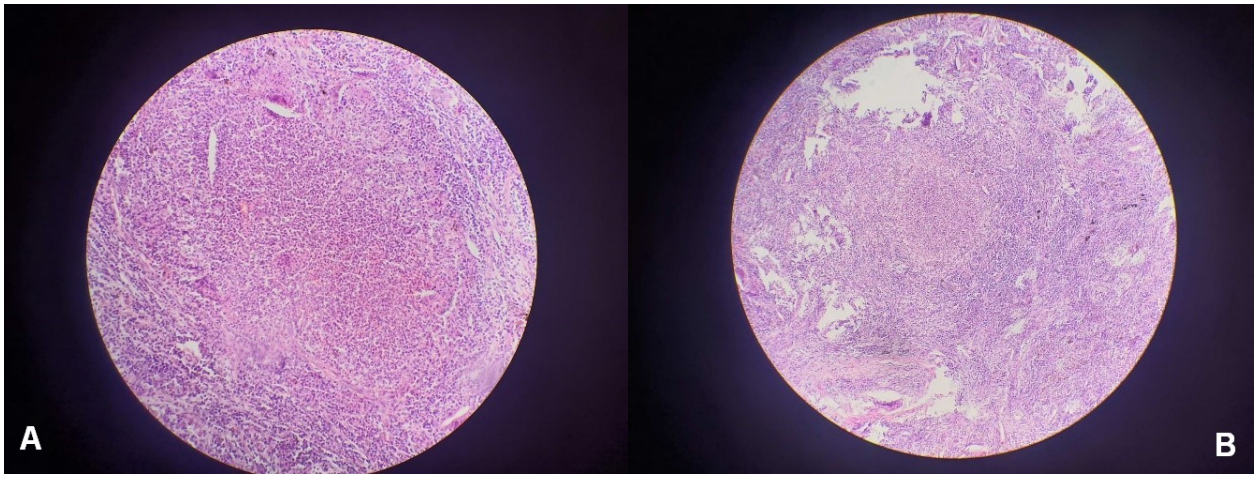

Fig. 10 – Abscessed inflammation: hematoxylin-eosin staining magnification, ×10 (A) and ×4 (B).

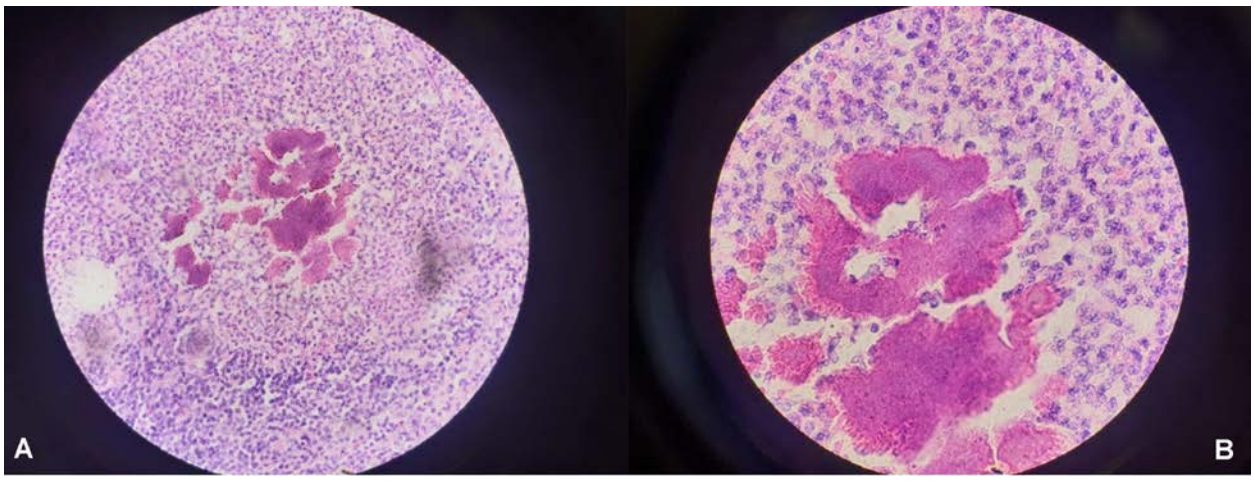

Fig. 11 – Actynomices colonies: hematoxylin-eosin staining magnification, ×40 (A) and ×60 (B).

The postoperative course went well, the chest drain was removed after establishing the aerostasis, and the patient was discharged home for treatment 2 days after the intervention.

A month after the surgery, the patient was admitted to the Clinic for Infectious and Tropical Diseases, Belgrade, Serbia, for evaluation and initiation of antibiotic therapy for pulmonary actinomycosis. At the aforementioned clinic, the patient was fully examined to identify an immunosuppressive condition that may have contributed to the development of a lung infection. Numerous analyses were performed, including an ultrasound of the abdomen,

pelvis, and scrotum, which was normal, and esophagogastroduodenoscopy, which showed no pathological findings. MDCT of the paranasal cavity revealed polypoid masses in the left nasal passage and *deviatio septi nasi* on the right side. Ultrasound of the axilla was normal, stool testing for occult bleeding was negative, and immunological analyses showed no deviations from normal values.

He was treated with ceftriaxone and clindamycin for 4 weeks and discharged from the hospital with doxycycline for further home treatment (6 months). A follow-up MDCT of the thorax and abdomen was performed; there were no signs of residual or recurrent infection. At the control pulmonology outpatient examination, the patient reported no complaints and was in good general condition. He remained under follow-up by infectious disease and pulmonary specialists for two years with no ongoing pharmacological therapy.

Discussion

PA is a very rare condition, with an estimated incidence of approximately 1 *per* 3,000,000 people a year. It is a chronic, slowly progressive bacterial infection caused by several species belonging to the *Actinomyces* genus. Among the six *Actinomyces* spp. known to be pathogenic in humans, *A. israelii* is the most commonly identified. In pulmonary forms of the disease, however, *A. graevenitzii* is most frequently reported as the causative agent [4].

Actinomycosis is often referred to as the "great imitator" because of its ability to mimic various other conditions. Nevertheless, it can be distinguished from infections caused by other non-acid-fast filamentous bacilli by the presence of sulfur granules, which are considered pathognomonic. Although the infection most commonly involves the oral and cervicofacial areas, it may also affect other anatomical sites, particularly in immunocompromised patients. PA usually develops following aspiration of oropharyngeal or gastrointestinal secretions into the lower airways [6]. Furthermore, this form of the disease is reported more frequently in developing regions than in developed countries [7].

It is assumed in this case and in our patient that, due to inadequate oral hygiene and in the absence of an immunosuppressive state, there was a slow development of PA with the formation of a larger pulmonary infiltrate, one year after the mentioned dental intervention.

Clinical manifestations of PA are very nonspecific. They can be differentially diagnosed from chronic lung infections to neoplastic manifestations [8, 9]. The symptoms that are manifested also have a wide range. The most common symptoms are fever, very often subfebrile, weight loss, productive cough, chest pain, and hemoptysis [4]. Clinical and radiological signs can mimic various lung diseases, from tuberculosis to malignant lung diseases [10]. The diagnosis of PA is established based on histological and microbiological examination of a sample obtained *via* bronchoscopy or after surgical intervention [11].

Indications for surgical intervention are the existence of severe invasive disease, infection of critical areas, as well as the existence of massive refractory hemoptysis. Surgical treatment is indicated in patients with involvement of, or proximity to, the main blood vessels or large airways, as well as in cases of greater involvement of the lung parenchyma. The primary goal of surgical intervention is to reduce the extent of the disease (tumor mass) and prevent life-threatening complications–in this case, involvement of almost the entire right upper lobe, accompanied by a long-standing cough and pain syndrome. The mass in the right upper lobe had the appearance of a neoplastic lesion, which had not previously received HP verification [12].

Since the diagnosis could not be established by repeated TBB, the lesion appeared as tumorous on MDCT, and the patient's symptoms persisted, VATS was performed.

Due to the processing of the sample for HP analysis, subsequent microbiological processing at the Institute of Microbiology, was not possible in this case, which would involve microscopic examination (Gram's staining to observe filamentous, Gram-positive bacteria arranged in characteristic aggregates–the so-called "sulfur granules"), as well as cultivation on Brucella blood agar in anaerobic conditions, with additional identification and differentiation of the most common causative agents of actinomycosis, including *A. israelii*, *A. naeslundii*, *A. odontolyticus*, *A. meyeri*, and *A. graevenitzii*.

Treatment of PA involves the use of antimicrobial therapy with or without surgery. Surgical treatment of PA requires removal of infected tissue, which can be performed by VATS or open surgery. In severe disease, segmentectomy or even lobectomy is sometimes indicated. Surgical treatment must be combined with antimicrobial therapy, because isolated surgical treatment as the only type of treatment is rarely successful [13]. In this case, our patient underwent an atypical resection of the right upper lobe. Once the pathologist called the *ex tempore* as benign, the lung resection was ended as atypical. Antibiotic therapy for mild to moderately severe disease includes oral phenoxymethylpenicillin, 2–4 g in two doses, or amoxicillin, 1.5–3 g daily in three or four doses. In cases where infection by additional pathogens is suspected, the use of amoxicillin with clavulanic acid in a dose of 1g twice a day *per os* is indicated. The duration of treatment should usually be continued for 1–2 months after the cessation of symptoms. The treatment usually lasts 2–6 months in mild forms of the disease. In severe forms of the disease, the use of high doses of parenteral antibiotics, benzylpenicillin or ceftriaxone is required. If there is any doubt about the presence of pathogenic bacteria, the use of piperacillin, tazobactam 4.5 g four times a day is recommended. The duration of intravenous therapy is 2–6 weeks, after which, upon clinical improvement, the patient is transferred to oral therapy. Oral treatment lasts between 6 and 12 months, depending on the severity of the disease and indicators of clinical improvement [14].

HP etiologically clarified the lesion in the right upper lobe of the lung after it was removed. Our patient had no primary or secondary immunodeficiency, so we concluded that the actinomycosis arose in the context of extensive dental interventions performed in the previous period.

According to Kim et al. [10], out of 94 analyzed cases, 50% of diagnoses were established through surgical biopsy, while bronchoscopic biopsy was successful in 25.5% of cases. Other authors report that the surgical method was twice as effective in establishing a diagnosis compared to bronchoscopy [15].

Conclusion

Actinomycosis of the lung is a very rare disease that can have an atypical clinical and radiological presentation. It very often imitates other diseases, including neoplastic processes in the lungs. In this regard, it requires a multidisciplinary approach, both diagnostic and therapeutic.

Conflict of interest

Authors declare no conflict of interest.

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LETTER TO THE EDITOR

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The Death of Alcathous in the *Iliad*: The First Verifiable Description of Penetrating Cardiac Trauma

(A comment on the paper: *Miloš Velinović†, Mile Vraneš**†, Biljana Obrenović-Kirćanski**‡, Svetozar Putnik**†, Aleksandar Mikić**†, Dragutin Savić**†, Radmila Karan§†, Nataša Kovačević-Kostić§†*. Penetrating wound of the heart manifested with peripheral embolism – case report. *Vojnosanit Pregl* 2012; 59(9): 803–5, and the author's response)**

Smrt Alkatoja u Ilijadi: Prvi verifikovani opis penetrantne trauma srca

(Komentar o članku: *Miloš Velinović**†, Mile Vraneš**†, Biljana Obrenović-Kirćanski**‡, Svetozar Putnik**†, Aleksandar Mikić**†, Dragutin Savić**†, Radmila Karan§†, Nataša Kovačević-Kostić§†*. Ustrelna povreda srca manifestovana perifernom embolijom. *Vojnosanit Pregl* 2012; 59(9): 803–5, i odgovor autora)

Comment

It is always important to expand knowledge related to the fascinating subject of thoracic trauma. In this regard, the case presented by Velinović and colleagues may be considered of great value, as it reports an unusual peripheral embolism at the level of the right common femoral artery resulting from a paradoxical embolism through an interatrial communication, secondary to an old penetrating thoracic trauma of the right hemithorax caused by a firearm [1].

However, in the aforementioned article, the authors state that "the first described cardiac trauma was reported by the Egyptians 5,000 years ago in the Edwin Smith Surgical Papyrus," a claim that is not entirely accurate. Although this document describes a total of 48 noteworthy cases demonstrating the medical and surgical knowledge of ancient Egyptian civilization, including both non-penetrating and penetrating thoracic injuries, none of them involves the heart as a directly affected organ [2].

Following a meticulous study of the historical origins of penetrating cardiac trauma (PCT), it can be concluded that Homer, in his epic poem The *Iliad*, was the first to describe this entity. In this classical Greek epic poem, dating to the 8th century BC and translated into multiple languages according to the interpretation and translational style of various authors, numerous thoracic injuries sustained in battle are described. After analyzing several of these translations and noting that they all coincide in their account of Book XIII, it may be argued that the death of Alcathous constitutes the first description of PCT in history [3]. This passage is rendered verbatim as follows: "*Λουπῆσεν δὲ πεσών, δόρυ δ' ἐν κραδίῃ ἐπεπήγει*" ("He fell with a dull thud, and the spear was driven into his heart"), in which the phrase "*ἐν κραδίῃ*" ("in the heart") is explicit [4].

Furthermore, it should be noted that many authors cite the death of Sarpedon, narrated in Book XVI, as the first historical event alluding to PCT–a claim that is likewise not entirely accurate. Some of the consulted translations mention the heart as the directly affected anatomical structure, whereas others describe different elements or fail to specify particular organs, referring instead to structures such as the mid-abdomen, the entrails, or simply the chest near the heart [3]. According to Friedrich [5], the translation derived from the interpretation of the Greek word *φρένες* does not provide an exact explanation that allows precise identification of the anatomical structure injured by the fatal wound sustained by Sarpedon in battle, which could be related to structures such as the heart, lung, diaphragm, liver, stomach, or spleen. In addition, Gutiérres notes that the term *φρένες* may be considered indeterminate or ambiguous and can be interpreted in various ways from an anatomical as well as physiological, psychological, and cognitive standpoint [6].

In conclusion, critical analysis of historical and philological sources allows us to affirm that the death of Alcathous, described in Book XIII of The *Iliad*, constitutes the first explicit and verifiable reference to penetrating cardiac trauma, as it unequivocally mentions direct involvement of the heart. This finding not only corrects historical inaccuracies frequently reproduced in medical literature but also underscores the value of classical texts as primary sources for understanding the early development of anatomical and traumatic knowledge, reinforcing the need for an interdisciplinary approach integrating medicine, history, and philology.

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Author's response

We thank the authors of the Letter to the Editor for their interest in our article and for contributing to the discussion on the historical origins of documented cardiac trauma. Scholarly debate on the foundations of medical knowledge is both welcome and necessary. However, we believe that the central argument presented in the Letter conflates literary narrative with scientific medical documentation, a distinction that requires clarification.

The Letter contends that Homer's *Iliad* contains the earliest reference to heart wounds and should therefore replace the source cited in our article. While this claim may be significant in a literary or cultural-historical context, it is methodologically unsound within the framework of medical historiography.

In epic literature–most notably in Homer's *Iliad*–descriptions of bodily injury function primarily as narrative devices serving poetic, symbolic, and dramatic purposes [1]. Although such passages refer to anatomical structures, including the heart, they lack diagnostic intent, systematic observation, therapeutic reasoning, and clinical applicability.

By contrast, the Edwin Smith Surgical Papyrus [2, 3] is a medical–surgical treatise. Its cases follow a structured format that includes examination, diagnosis, prognosis, and management, reflecting empirical clinical reasoning rather than metaphor or allegory.

This distinction between narrative descriptions of violence and analytical medical documentation of trauma is fundamental. As a scientific discipline, medical history does not establish historical "firsts" on the basis of mere narrative mention, but on methodology, intent, and epistemological framework [4-7].

Historians of medicine commonly apply several criteria when defining early scientific medical documents:

1. Systematic case presentation,
2. Anatomical specificity grounded in observation,
3. Prognostic reasoning based on outcomes,
4. Therapeutic or management intent,
5. Didactic purpose for medical practice.

The Edwin Smith Surgical Papyrus [2, 3] meets all of these criteria. Its trauma cases–particularly those involving the head, neck, and thorax–demonstrate an awareness of the lethality of chest injuries and implicitly recognize the heart as a vital organ whose damage is incompatible with survival.

The Homeric epics, by contrast, meet none of these standards [1]. Their anatomical references are incidental to narrative aims and cannot be retroactively classified as medical documentation without eroding the epistemological boundaries of medical science.

Our wording is also consistent with contemporary cardiology and trauma literature. Authoritative modern textbooks explicitly identify the Edwin Smith Surgical Papyrus [2] as the earliest medical description of traumatic cardiac injury. In the cardiac trauma chapter of Moss & Adams' Heart Disease in Infants, Children, and Adolescents [8], the papyrus is cited as the first description of penetrating cardiac wounds, whereas Homer's *Iliad* is mentioned only as a later literary source. Jagelavičius et al. [9], in a 28-year series of penetrating cardiac injuries, describe the papyrus as providing "the most ancient data about cardiac injuries". Major reviews of penetrating cardiac and thoracic trauma likewise begin their historical overviews with the Edwin Smith Surgical Papyrus as the earliest written description of cardiac or intrathoracic injury, even when they also mention Homeric passages, thereby treating the papyrus as the foundational medical source.

Coming from a cultural tradition rich in mythology and epic literature, we recognize the historical and symbolic importance of such works. From a scientific standpoint, however, we maintain that the Edwin Smith Surgical Papyrus remains the earliest extant medical–surgical document to address traumatic injuries of the chest–and, by implication, the heart–using empirical observation and clinical reasoning [3, 4]. Earlier literary texts, including Homer's *Iliad* [1], despite their vivid depictions of fatal chest wounds, remain literary rather than scientific and cannot be treated as medical sources within the discipline of medical history.

Accordingly, the source cited in our article remains appropriate, methodologically robust, and consistent with established historiographical standards.

Sincerely,
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ACKNOWLEDGEMENTS

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Article with more than 6 authors

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Volume with a Supplement

Smith JA, Brown LM. Effects of vitamin D on immune response. J Nutr Sci 2024; 15(Suppl 2): S45–53.

Issue with a Supplement

Zhou Q, Shi R, Kopjar B, Wang H, Chen D, Li H, et al. Adjacent Intervertebral Disc Changes in Patients with Isobar Semirigid Dynamic Stabilization System. Global Spine J 2017; 4(1 Suppl): s-0034-1376699.

Volume with Part (Pt)

Ozben T, Nacitarhan S, Tuncer N. Plasma and urine sialic acid in non-insulin dependent diabetes mellitus. Ann Clin Biochem 1995; 32(Pt 3): 303–6.

Issue with Part (Pt)

Poole GH, Mills SM. One hundred consecutive cases of flap lacerations of the leg in ageing patients. N Z Med J 1994; 107(986 Pt 1): 377–8.

Issue with no Volume

Turan I, Wredmark T, Fellander-Tsai L. Arthroscopic ankle arthrodesis in rheumatoid arthritis. Clin Orthop 1995; (320): 110–4.

No Volume or Issue

Browell DA, Lennard TW. Immunologic status of the cancer patient and the effects of blood transfusion on antitumor responses. Curr Opin Gen Surg 1993: 325–33.

Pagination with Roman numerals

Fisher GA, Sikic BI. Drug resistance in clinical oncology and hematology. Introduction. Hematol Oncol Clin North Am 1995; 9(2): xi–xii.

Book

Printed Book

Ritter JM, Flower RJ, Henderson G, Loke YK, MacEwan D, Robinson E, et al. Rang & Dale's Pharmacology. 10th ed. London: Elsevier; 2023. p. 3630.

Book in electronic format

Shreeve DF. Reactive attachment disorder: a case-based approach [Internet]. New York: Springer; 2012 [cited 2012 Nov 2]. 85 p. Available from: http://dx.doi.org/10.1007/978-1-4614-1647-0

Chapter

In an edited book

Metcalf CS, Smith MD, Wilcox KS. Pharmacotherapy of the Epilepsies. In*: Brunton LL, Knollmann BC,* editors. Goodman & Gilman's The pharmacological basis of therapeutics. 14th ed. NY: McGrawHill; 2023. p. 385–411.

In an edited electronic (online) book

Halpen-Felsher BL, Morrell HE. Preventing and reducing tobacco use. In: *Berlan ED, Bravender T,* editors. Adolescent medicine today: a guide to caring for the adolescent patient [Internet]. Singapore: World Scientific Publishing Co.; 2012 [cited 2012 Nov 3]. Chapter 18. Available from: http://www.worldscientific.com/doi/pdf/10.1142/9789814324496_0018

Website

Homepage

Diabetes Australia. Diabetes globally [Internet]. Canberra ACT: Diabetes Australia; 2012 [updated 2012 June 15; cited 2012 Nov 2]. 85 p. Available from: http://www.diabetesaustralia.com.au/en/Understanding-Diabetes/Diabetes-Globally/

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Australian Medical Association [Internet]. Barton ACT: AMA; c1995-2012. Junior doctors and medical students call for urgent solution to medical training crisis; 2012 Oct 22 [cited 2012 Nov 2]; [about 3 screens]. Available from: https://ama.com.au/media/junior-doctors-and-medical-students-call-urgent-solution-medical-training-crisis

Conference Proceedings

Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

Article from Conference Proceedings

Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: *Lun KC, Degoulet P, Piemme TE, Rienhoff O,* editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6–10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561–5.

Dissertation

Knežević D. The importance of decontamination as an element of complex therapy of poisoning with organophosphorous compounds [Ph.D. Thesis]. Belgrade: School of Veterinary Medicine; 1988. (Serbian)

Other published articles

News article

Vujadinović J. The inconsistency between federal and republican regulation about pharmacies. In between double standards. Borba 2002 February 28; p. 5. (Serbian)

Holy Bible

Serbian Bible. Belgrade: British and Foreign Biblical Society; 1981. Book of Isaiah 2: 19–22. (Serbian)

Dictionaries and similar references

Kostić AĐ. Multilingual Medical Dictionary. 4th Ed. Belgrade: Nolit; 1976. Erythrophobia; p. 173–4.

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Рад који не испуњава услове овог упутства не може бити разматран и биће враћен ауторима да га допуне и исправе**.**

Аутори рада преносе своја ауторска права на издавача часописа Министарство одбране Републике Србије, Универзитет одбране **након прихватања рада за објављивање у ВСП**.

ВСП се придржава препорука Међународног комитета уредника медицинских часописа (*International Committee of Medical Journal Editors* – ICMJE), *Препоруке за спровођење, извештавање, уређивање и публиковање научних радова у медицинским часописима* (доступно на https://www.icmje.org/recommendations/).

ВСП је доступан у режиму отвореног приступа. Сви чланци могу се бесплатно преузети са сајта часописа и користити у складу са лиценцом **Creative Commons Autorstvo-Deliti pod istim uslovima (CC BY-SA) (**https://creativecommons.org/licenses/by-sa/4.0/deed.en**).**

СЛАЊЕ РУКОПИСА

Рукопис рада и сви прилози уз рад достављају се **као један документ** (прилози су инкорпорирани у текст и позиционирани на крају рукописа иза одељка Литература) искључиво електронски преко система за пријављивање *Aseestant*. Ради очувања квалитета фотографија, препоручује се достављање слика и као посебних фајлова, јер Word може смањити њихову резолуцију, како би се избегла компресија слика и евентуални губитак квалитета.

Сви аутори и рецензенти морају бити регистровани корисници система са јединственом е-маил адресом. Регистрацију је могуће извршити на: http://aseestant.ceon.rs/index.php/vsp/user. Техничко упутство за коришћење система електронске пријаве доступно је на: https://aseestant.ceon.rs/index.php/vsp/about/submissions.

Уколико имате проблем са подношењем рукописа путем платформе *Aseestant* можете се обратити за помоћ Редакцији часописа слањем е-мејла на адресу: vsp@vma.mod.gov.rs.

ОПШТА УПУТСТВА

ВСП објављује радове који до сада нису претходно објављени (у целини или делом), који се не разматрају за објављивање нити су прихваћени за објављивање у неком другом часопису.

ВСП не разматра радове који су претходно објављени као препринт верзије.

Часопис прихвата и радове чији су резултати претходно приказани на научним или стручним скуповима и објављени у виду апстракта, под условом да ти резултати нису објављени са DOI бројем (нпр. проширени апстракт у додатку неког часописа).

Уколико је део резултата поднетог рукописа претходно саопштен на научном/стручном скупу или је део докторске дисертације, у Пропратном писму Уредништву потребно је навести званичан назив скупа, место и време одржавања, и да ли су саопштени резултати публиковани и у којој форми (нпр. исти или другачији наслов или сажетак), а у Напомени на крају рукописа то треба посебно назначити.

Радови се објављују на енглеском језику. Поједине категорије радова (нпр. историја медицине/стоматологије/фармације) се по одлуци Уредништва ВСП могу објавити и на српском језику. Све категорије рукописа осим категорија уводник, писмо уреднику, истраживачко писмо, приказ књиге, извештај са научног или стручног скупа се објављују са апстрактима на српском и енглеском језику (у склопу рукописа). О структури и обиму апстракта видети детаљније у одељку Апстракт овог Упутства.

За писање рукописа користити програм *Word*, фонт *Times New Roman*, величину слова 12, проред 1,5. Величину странице подесити на формат А4, са левом маргином од 4 цм а преостале три 2 цм. Текст куцати без дељења речи (хифенације), а после сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*.

Подаци о коришћеној литератури у тексту означавају се арапским бројевима у суперскрипту, редоследом којим се појављују у тексту.

Странице нумерисати редом у доњем десном углу, почев од прве стране (изузимајући насловну страну).

При писању текста на енглеском језику придржавати се језичког стандарда *American English*. Обавезно је коришћење међународног система мера (SI). Изузетак чине крвни притисак (mm Hg) i temperatura (°C).

Приликом писања користе се стандардне скраћенице. Избегавати скраћенице у наслову и апстракту осим уколико је неопходно. Пун назив са скраћеницом у загради наводи се у њеном првом помињању, а даље у тексту само скраћенице, како у апстракту тако и у главном тексту. У закључку рада (не апстракта) нема скраћеница.

Не користити комерцијална имена лекова и других препарата, а уколико је то неопходно уз њихове називе обавезно навести и генеричка имена. Уређаји (апарати) се означавају фабричким називима, а податке о произвођачу (назив и место) навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или субскрипту.

Избегавати фонтове *bold* и курзив (*italic*) јер су резервисани за поднаслове. Изузеци су обавезно писање курзивом оних назива који се тако морају писати (нпр. гени или стране речи - латински).

Групе испитаника морају бити јасно дефинисане и доследно именоване кроз цео рад. За исти појам користити један, јединствен термин кроз цео рад. У одељку Резултати избегавати реченице које почињу са: „Табела X показује “ или „Слика X приказује“. Реченица треба да опише резултат, а ознака табеле или слике да стоји у загради на крају описа. Реченице не би требало почињати скраћеницом, бројем или датумом. Избегавати предугачке реченице које умањују јасноћу текста и дати предност краћим јасним реченицама. Закључак формулисати новим реченицама, без преписивања већ изречених. Превод радова на енглески језик посредством *Google Translate* може изазвати неразумевање текста и стога се не препоручује.

У избору кључних речи користити *Medical Subject Headings – MeSH* (https://www.nlm.nih.gov/mesh/meshhome.html). Кључне речи у прихваћеном рукопису не подлежу ауторској коректури, пошто су оне дескриптори из Тезауруса које одређују стручни индексери.

ОБАВЕЗНА ПРАТЕЋА ДОКУМЕНТА

ИЗЈАВА АУТОРА И АУТОРСТВО

За сваки рукопис који се подноси на разматрање за објављивање у ВСП неопходно је да аутор(и) достави(е) Образац за изјаву о ауторству (Изјаву аутора) да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, да су рукопис прочитали и одобрили сви аутори који испуњавају критеријуме ауторства, и контакт податке свих аутора у раду (имејл адресу, број мобилног телефона). У овом обрасцу се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. Сви аутори морају Изјаву аутора потписати својеручно.

За додатне информације о различитим врстама сукоба интереса видети препоруке Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME;* http://www.wame.org*)*.

ВСП поштује препоруке критеријума за ауторство које даје ICMJE (https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). Ауторство се заснива на испуњењу сва четири критеријума: значајном доприносу концепцији рада, добијању резултата или анализи/тумачењу резултата; критичкој ревизији рукописа од знатног интелектуалног значаја; одобрењу финалне верзије рукописа која ће бити објављена и преузимању одговорности за све аспекте објављеног садржаја. Сви други учесници који су допринели изради рада, али нису испунили прописане критеријуме требало би да буду наведени у Захвалници уз прецизирање доприноса раду. Потребно је да особе наведене у Захвалници дају писмену сагласност.

ЕТИЧКА САГЛАСНОСТ

Сва истраживања која укључују људе и/или хумани материјал морају бити спроведена у складу са препорукама ICMJE (https://www.icmje.org/recommendations/browse/roles-and-responsibilities/protection-of-research-participants.html) и Хелсиншком декларацијом, ревизија 2024 (https://www.wma.net/policies-post/wma-declaration-of-helsinki/). Скенирану страну дозволе Етичке комисије (ЕК) надлежне институције које је одобрила истраживање, на којој се види датум издавања и предмет истраживања, аутори су у обавези да доставе истовремено са рукописом. Дозвола ЕК се доставља на језику на коме је издата и енглеском језику (може и оверена копија).

У одељку Методе мора бити наведено да је студија одобрена од стране надлежног ЕК, уз навођење назива институције и броја одлуке, као и да је спроведена у складу са етичким принципима за истраживања која укључују људе и/или хумани материјал.

Анонимност пацијената мора бити заштићена у складу са ICMJE препорукама. За сва истраживања која укључују податке о пацијентима који омогућавају директну или индиректну идентификацију, аутори су обавезни да прибаве писани пристанак информисаног пацијента, да у рукопису назначе да је пристанак пацијента прибављен, и да га по потреби доставе Уредништву.

У случају истраживања на животињама, аутори су дужни да доставе одобрење надлежног ЕК који води бригу о поштовању међународних стандарда о употреби лабораторијских животиња у истраживачке сврхе.

Уредништво може одбити радове за које процени да нису изведени у складу са међународним етичким стандардима.

РЕПРОДУКОВАЊЕ ПРЕТХОДНО ОБЈАВЉЕНОГ ЗАШТИЋЕНОГ МАТЕРИЈАЛА И/ИЛИ НЕОБЈАВЉЕНОГ ТУЂЕГ МАТЕРИЈАЛА

Уколико се користе претходно објављене илустрације (фотографије, схеме) уз обавезно цитирање извора преузимања потребно је доставити дозволу (писано одобрење часописа у коме су објављене) за њихову објаву у ВСП. Уколико се користе туђе необјављене илустрације (фотографије, схеме) потребно је доставити дозволу аутора илустрација, за њихову објаву у ВСП.

ПЛАГИЈАРИЗАМ

Од 2012. године сви рукописи достављени на разматрање у ВСП подвргавају се провери на потенцијални (ауто)плагијаризам посредством *SCIndeks Assistant – Cross Check* (*iThenticate*). Рукописи код којих се докаже (ауто)плагијаризам биће одбијени. У зависности од степена и врсте утврђеног (ауто)плагијаризама ауторима се може изрећи забрана објављивања у ВСП-у (различите дужине трајања), уз обавештење надлежних тела у институцијама у којима аутори раде и релевантних професионаних удружења.

КОРИШЋЕЊЕ AI

Генеративна вештачка интелигенција (*artificial intelligence*-AI) или технологије које користе помоћ AI (AI-потпомогнуте) могу се користити само уз поштовање начела транспарентности (употреба AI мора бити јасно наведена у рукопису), одговорности (аутори остају у потпуности одговорни за тачност и оригиналност садржаја), проверљивости (сви учесници у публицистичком процесу морају проверити да AI није унела измишљене податке, цитате или тврдње) и поверљивости (ауторима и рецензентима је забрањено учитавање рукописа поднетих у ВСП у јавне AI сервисе).

Употреба AI алата је допуштена само за ограничене језичке и техничке интервенције у тексту рукописа: исправку граматике и правописа, стилско дотеривање ауторског текста, помоћ при форматирању, техничку асистенцију (попут исправљања кода). Аутори могу користити AI алате искључиво за креирање AI-потпомогнутог, али не и AI -генерисаног садржаја.

Аутори који су користили AI-потпомогнут садржај у обавези су да потпуно и тачно наведу употребу AI алата (тачан назив AI алата, датум приступа, коришћене упите и сврху употребе), гарантују оригиналност научног доприноса, избегавају било какву фабрикацију или манипулацију и поштују правила научне етике. Информације о коришћењу AI се наводе у одељку Методе или Захвалница.

Забрањено је користити AI алате за генерисање већег дела садржаја рукописа, креирање научних идеја, података и резултата, анализу и интерпретацију резултата, формирање закључака, измену слика, табела или графикона (укључујући графичке сажетке), измену података или референци.

Недвосмислено утврђена недопуштена употреба AI за последицу има одбијање рада.

AI ни у ком случају не може бити аутор или коаутор рада, нити може као аутор бити цитиран у одељку Литература.

Ради заштите поверљивости, ниједан део необјављеног истраживања достављеног ВСП не сме бити унет у велики језички модел од стране аутора или рецензента.

Аутори који су користили неки од AI алата су у обавези да приликом подношења рукописа поднесу и Изјаву о коришћењу AI.

ТИПОВИ РУКОПИСА

У ВСП се објављују следеће категорије и типови рукописа и саопштења: уводник, оригинални рад, претходно саопштење, кратко саопштење, приказ случаја и серија случајева, општи (наративни) преглед литературе, мини преглед, систематски преглед литературе, мета-анализа, систематски преглед литературе са мета-анализом, актуелна тема, у фокусу, рад из историје медицине/стоматологије/фармације, писмо уреднику, истраживачко писмо, клиничко истраживање, извештај са конгреса и научног скупа, приказ књиге, *In memoriam* и други прилози.

ОРИГИНАЛНИ ЧЛАНАК

Приказује нова и значајна открића у одређеној области уз детаљан опис коришћених метода истраживања, добијених резултата и изведених закључака. Листа референци треба да укључи најновије и најважније референце из области рада.

ПРЕТХОДНО САОПШТЕЊЕ

Представља приказ истраживања која нису завршена, са налазима који захтевају додатна истраживања и валидацију пре коначних закључака, али су добијене информације од интереса за научну и стручну јавност. Садржи сва поглавља као оригинални научни чланак, али у знатно скраћеном обиму. Аутори се подстичу да касније објаве пуну оригиналну научну студију са комплетним, валидираним подацима и свеобухватном анализом.

КРАТКО САОПШТЕЊЕ

Представља завршено истраживање које је мало по обиму, уско фокусирано са јасним закључцима на основу представљених резултата. Садржи сва поглавља као оригинални научни чланак, али у знатно скраћеном обиму. Сматра се коначном публикацијом тог специфичног, малог истраживања. Не може се поново објавити као чланак пуног обима (иако се подстиче накнадно истраживање које се надовезује на њега).

ПРЕГЛЕДНИ ЧЛАНЦИ

ОПШТИ (НАРАТИВНИ) ПРЕГЛЕД ЛИТЕРАТУРЕ

Преглед, критичка анализа и синтеза постојећих научних сазнања о изабраној теми. Аутори обухватају сву доступну припадајућу литературу за одређени временски период, приказују резултате релевантних истраживања, идентификују недостатке, ограничења или контроверзе и указују на правце будућих истраживања, дајући своје виђење проблема у виду закључног става. Аутори чланка ове категорије могу бити они који су објавили минимално пет радова публикованих у часописима с рецензијом (M20) из области прегледног рада.

МИНИ ПРЕГЛЕДНИ ЧЛАНАК

Сажет преглед постојеће литературе и најновијих достигнућа унутар дефинисаних аспеката одређене истраживачке области и њени нови и/или актуелни правци развоја.

СИСТЕМАТСКИ ПРЕГЛЕД ЛИТЕРАТУРЕ

Синтеза претходно објављених истраживања о одређеној теми коришћењем јасно дефинисаних и унапред одређених методолошких поступака за селекцију и евалуацију. Аутор мора да користи релевантне базе података, постави критеријуме укључивања и искључивања студија и примени транспарентну методологију.

МЕТА-АНАЛИЗА

Користи статистичке методе за комбиновање квантитативних података из више примарних студија како би се идентификовали општи трендови и проценила снага доказа о одређеној теми. Аутор мора да користи релевантне базе података, дефинише критеријуме за укључивање и искључивање и примени транспарентну и репродуцибилну методологију. Неопходно је јасно дефинисање истраживачког питања (PICOS оквир), навођење смерница за одабир и дијаграма тока за селекцију студија (PRISMA).

СИСТЕМАТСКИ ПРЕГЛЕД ЛИТЕРАТУРЕ СА МЕТА-АНАЛИЗОМ

Комбинује квалитативну и квантитативну синтезу, користећи статистичке технике за сумирање квантитативних резултата а квалитативну синтезу за описне/наративне налазе. Аутор мора користити релевантне базе података, јасно дефинисати критеријуме за укључивање и искључивање студија, и применити транспарентну и репродуцибилну методологију. Истраживачко питање мора бити јасно дефинисано према PICOS оквиру, уз навођење коришћених смерница за извештавање (нпр. PRISMA) и укључивање PRISMA дијаграма тока за приказ селекције студија.

АКТУЕЛНА ТЕМА

Разматра савремено, нерешено или контрадикторно питање од теоријског и практичног значаја, уз изношење сопствених резултата истраживања или најновијих важних података из литературе. Конструкција чланка је слободна а пожељне су кратке закључне напомене са јасном поруком.

У ФОКУСУ

Тематска, фокусирана анализа и/или кратак осврт на научни проблем који је у тематској области часописа, а који обрађује питање од значаја за научну заједницу и ширу стручну јавност.

КАЗУИСТИКА

ПРИКАЗ СЛУЧАЈА и СЕРИЈА СЛУЧАЈЕВА (≥4, ≤9)

Приказ случајева са ретком и необичном дијагнозом, дијагностичким процесом, стратегијама лечења, клиничким током, или исходом лечења, који могу бити од користи за клиничку праксу и медицинско образовање. Приликом писања потребно је користити CARE смернице (https://www.care-statement.org/writing-a-case-report). Неопходан је пристанак информисаног пацијента.

УВОДНИК

Уводници су нерецензирани текстови главног и одговорног уредника и/или чланова Уредништва намењени најави новог волумена, тематског броја, садржаја који су од значаја за струку и/или институције чијим члановима је часопис намењен као и уреднички текстови по позиву. Уводници не треба да садрже необјављене или оригиналне податке, а морају укључити изјаву о сукобу интереса.

ПИСМО УРЕДНИКУ

Нерецензирани коментар/критика текста објављеног у ВСП. Пишу се у слободној форми, уз евентуално навођење података из литературе. Не смеју садржати необјављене резултате. Објављују се према одлуци главног и одговорног уредника.

ИСТРАЖИВАЧКО ПИСМО

Кратки приказ оригиналног истраживања, који садржи увод, методе, резултате и дискусију у сажетом облику (без поделе у посебне целине са поднасловима) и максимално до 2 прилога (табеле/слике). Не садржи апстракт и кључне речи али мора да испуни све опште услове за разматрање рукописа (укључујући процес рецензије).

ИСТОРИЈА МЕДИЦИНЕ/СТОМАТОЛОГИЈЕ/ФАРМАЦИЈЕ

Материјал значајан за расветљавање појединих догађаја и/или приказ значајних личности из историје медицине/стоматологије/фармације, а посебно војне медицине/стоматологије/фармације.

КЛИНИЧКО ИСТРАЖИВАЊЕ

Оригинална рандомизована контролисана испитивања и опсервационе студије утицаја једног или више средстава или мера на исход здравља људи, клиничку праксу и здравствену политику. Рукописи морају бити припремљени у складу са међународним смерницама (нпр. CONSORT – https://www.consort-spirit.org/ или STROBE – https://www.strobe-statement.org/) и регистрована у неком од међународно признатих јавних регистара (нпр. ClinicalTrials.gov).

ПРИКАЗ КЊИГЕ

Садржи библиографске податке о публикацији (аутори, изворни наслов, издавач, место и година издања), њен кратак садржај и критичке коментаре садржаја, стила и значаја књиге у датој области. Рукопис не сме бити дужи од 2 странице.

ИЗВЕШТАЈ СА НАУЧНОГ ИЛИ СТРУЧНОГ СКУПА

Приказ активности научног или стручног скупа, уз истицање најважнијих реферата или закључака, односно препорука од значаја за шири круг читалаца ВСП.

ОБИМ РУКОПИСА

Целокупни рукопис рада чине: насловна страна, апстракти на српском и енглеском језику са кључним речима, главни текст рада, захвалност (по потреби), списак литературе, прилози (табеле, слике, графикони, схеме, цртежи).

Обим рукописа за категорије оригинални рад, општи (наративни) преглед литературе, систематски преглед литературе, мета-анализа, систематски преглед литературе са мета-анализом износи до 5 000 речи.

Обим рукописа за категорије мини преглед, претходно саопштење, кратко саопштење, приказ случаја, серија случајева, актуелна тема, клиничко истраживање, историја медицине/стоматологије/фармације износи до 3 000 речи.

Рукописи за остале категорије/рубрике могу имати највише 1 500 речи.

ПРИПРЕМА РАДА

НАСЛОВНА СТРАНА

На првој страници рукописа треба навести следеће:

1. Наслов рада без скраћеница;
2. Пуна имена и презимена аутора (без титула, уз навођење ORCID броја за све ауторе који га имају) са ознакама следећим редом ***, †, ‡, §, ‖, ¶, **, †† …** итд.
3. Пун званичан назив установа у којима аутори раде, место и државу у којој се установе налазе (знаци *, †, ‡, §, ‖, ¶, **, †† … итд.показују редом установе у којима аутори раде);
4. На дну странице навести име и презиме, адресу за контакт, е-маил адресу и број телефона (мобилног/*Viber* или *WhatsApp*) аутора задуженог за кореспонденцију.

АПСТРАКТ

На другој страни рада пишу се апстракт и кључне речи. Апстракт се пише кратким и јасним реченицама. За категорије оригинални рад, претходно саопштење, кратко саопштење, систематски преглед литературе са метаанализом, мета-анализа, клиничко истраживање, апстракт је структурисан и треба да има следеће делове: Увод/Циљ, Методе, Резултати, Закључак. Сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) и ниво статистичке значајности. Закључак мора бити директно повезан са резултатима рада. Обим апстракта не сме да пређе 300 речи.

За категорије приказ случаја и серија случајева апстракт има следећу структуру: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак. Сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Обим апстракта не сме да пређе 250 речи.

За остале категорије радова, општи (наративни) преглед литературе, мини преглед, систематски преглед литературе, актуелна тема, у фокусу, историја медицине/стоматологије/фармације апстракт нема посебну структуру и не сме да пређе 200 речи.

Водити рачуна да српска и енглеска верзија апстракта буду међусобно тачни и прецизни преводи. Ниједна реченица не сме постојати у једној верзији а да није преведена у другој.

КЉУЧНЕ РЕЧИ

Испод апстракта навести пет до седам релевантних кључних речи или израза који указују на садржај рада. Препорука је да се не понављају речи из наслова рада. У избору кључних речи користити *Medical Subject Headings – MeSH* (https://www.nlm.nih.gov/mesh/meshhome.html).

СТРУКТУРА ГЛАВНОГ ТЕКСТА РАДА

Неопходно је да оригинални рад, претходно саопштење, кратко саопштење, мета-анализа, систематски преглед литературе са мета-анализом, клиничко истраживање садрже поглавља: Увод (кратак приказ предмета истраживања уз навод циља рада у последњем пасусу), Методе (прецизан опис одабира испитаника и примењених метода, укључујући статистичке методе, број дозволе сагласности надлежног ЕК), Резултати (приказани логичким редоследом без дуплирања приказа истих резултата на више начина), Дискусија (без понављања података који су већ наведени у одељку Резултати; дискутовати само добијене налазе довођењем у везу са другим релевантним студијама, повезати дискусију и закључке са циљевима рада, по потреби нагласити лимитације истраживања), Закључак (који проистиче из резултата датог истраживања), Захвалница (по потреби), Литература.

Рукописи из категорија општи (наративни) преглед литературе, мини преглед, систематски преглед литературе, актуелна тема, у фокусу садрже следеће целине: Увод (са одговарајућим поднасловима), Закључак, Литература.

Рукописи из категорије приказ случаја, серија случајева садрже следеће целине: Увод (циљ рада навести као последњи пасус Увода), Приказ болесника (идентитет болесника мора остати анониман), Дискусија, Литература.

Приказ болесника не сме имати више од пет аутора.

УПИТНИЦИ (Questionnaires)

Сви коришћени упитници који су употребљени као мерни инструменти за било који од испитиваних параметара, морају бити преведени на језик говорног подручја испитаника уз навођење доказа о извршеној валидацији и културолошкој адаптацији поднебљу испитаника.

ПРИЛОЗИ

Прилоге чији број треба да буде усклађен са дужином текста поставити на крај главног текста рукописа иза Литературе, а у самом тексту јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

Табеле

Наслов треба написати изнад табеле, а објашњења (легенду) испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле израдити искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће је чинити. Куцати фонтом *Times New Roman*, величином слова 12, с једноструким проредом. Табеле морају бити јасне и имати све елементе неопходне за правилно разумевање шта је у њима приказано. Уколико приказане вредности имају „опсег“ или „референтне вредности“, то се мора додати.

У легенди испод табеле треба објаснити све скраћенице наведене у табели и све ознаке (нпр. слова у суперскрипту или болдоване вредности). Такође, неопходно је прецизирати примењене статистичке методе.

Слике (илустрације)

Под сликама подразумевамо све облике графичких прилога (фотографије, цртежи, схеме и графикони). Слике треба уградити у рукопис на крају текста, после литературе и после табела (ако их има). Слике се означавају арапским бројевима према редоследу навођења у тексту. Велика слова А, Б, Ц итд. треба користити за означавање делова вишеделних слика. Слова, бројеви и симболи треба да су јасни и уједначени, а довољне величине да приликом умањивања буду читљиви. Додаци приказани на сликама морају бити сачувани као фотографије (не као измењиви графички елементи), тако да се њихов положај не може мењати, како би се обезбедила тачност података приказаних на слици. Примају се искључиво дигиталне фотографије са минималном резолуцијом од 300 *dpi* и формата JPEG, PNG или PDF. Слике које не задовољаавају наведене услове неће бити прихваћене за објаву. Димензије достављених слика би требало да буду приближне димензијама у којима ће слика бити објављена. Уколико аутори нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини и као такве их доставити. Сви подаци на схемама и графиконима треба да буду исписани безсерифним фонтом ради лакше читљивости (нпр. *Arial*, *Helvetica*), величина слова не мања од 10 *pt*. Мерне јединице и скале морају бити јасно назначене. Децимални бројеви на графиконима морају бити приказани са тачком, а раздвајање хиљада мора бити означено зарезом (нпр. 1,234.56).

Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видео-приказа у е-издању и објављена у штампаном издању, као и линк ка платформи где је видео већ постављен.

У легенди испод илустрација треба објаснити све скраћенице, симболе, бројеве или слова који се користе за објашњење појединих делова слике. У случају графикона прецизирати примењене статистичке методе (по потреби), а код фотомикрографије навести детаље о врсти коришћеног бојења и увећању.

Уколико се приказују фотографије особа (болесника), лик мора бити „замућен“ или је потребно обезбедити писану дозволу лица са фотографије за њено коришћење. На прилозима (снимци рендгена, скенера, ултразвука, итд.) потребно је уклонити све што може да идентификује болесника. Уколико је слика већ негде објављена потребно је цитирати извор уз писано одобрење ако се ради о заштићеном материјалу.

СКРАЋЕНИЦЕ

Скраћенице користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (нпр. ДНК). За сваку скраћеницу, осим стандардне јединице мере, навести пун назив при првом навођењу у тексту (укључујући апстракт). У наслову и апстракту избегавати коришћење скраћеница, у наслову их користити само ако су неопходне. За појмове који се у тексту помињу више од три пута препоручује се увођење одговарајућих скраћеница.

ДЕЦИМАЛНИ БРОЈЕВИ

У тексту рада на енглеском језику децималне бројеве писати са тачком (нпр. 22.7), а у тексту на српском језику са зарезом (нпр. 22,7). Кад год је то могуће, број заокружити на једну децималу и писати доследно кроз цео рад (нпр. ако је једна вредност 32.2, све остале морају имати једну децималу, нпр. 32.0).

ЈЕДИНИЦЕ МЕРА

Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – m, килограм (грам) – kg (g), литар – L) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), притисак крви у милиметрима живиног стуба (mm Hg). Резултате клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (SI).

ЗАХВАЛНИЦА

Изнети допринос особе којој треба одати признање, али која не испуњава критеријуме за ауторство. Навести финансијску помоћ (спонзорства, стипендије, опрема и друго), као и назив пројекта у оквиру кога је истраживање спроведено.

СТАТИСТИЧКА АНАЛИЗА

У одељку Методе детаљно описати примењене статистичке методе како би била омогућена провера исправности њихове примене и репродукција анализе. Резултати морају бити нумерички јасно приказани уз одговарајуће показатеље варијабилности и поузданости (нпр. стандардна девијација, стандардна грешка, интервал поверења). Прецизирати тип студије и описати начин на који је изведена. Навести критеријуме укључења и искључења. Навести софтвер и верзију компјутерског програма у коме је извршена статистичка обрада података. У одељку Резултати као и у легендама табела и/или прилога навести статистички метод који је коришћен за анализу приказаних резултата. Вредности *p* се увек пишу са почетном нулом (нпр. $p > 0.05$ а не $p > .05$).

ЛИТЕРАТУРА

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту (укључујући табеле и легенде прилога). Препоручује се да већина цитираних радова буде млађа од десет година. Препоручује се да број цитираних оригиналних радова буде најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Сви радови, без обзира на језик извора, цитирају се на енглеском језику, а изворни језик наводи се у загради, иза цитиране референце.

Сви подаци о цитираној литератури морају бити тачни, а цитирани радови лако приступачни читаоцима. Уз сваку референцу навести DOI број. Препоручује се цитирање само радова објављених у часописима које индексирају *Current Contents, Index Medicus* (*Medline*), *Excerpta Medica, Scopus, Web of Science*.

Није дозвољено цитирање апстраката, секундарних публикација, усмених саопштења, необјављених радова, службених и поверљивих докумената, Википедије, препринт објава и *in press* чланака, повучених радова (*retracted article*), радова објављених у предаторским часописима.

Приликом цитирања сајтова, не може се цитирати насловна страна већ се мора цитирати она страна са које је информација преузета. Свака наведена референца мора бити доступна за проверу *online*. Уколико референца не постоји на интернету (нпр. архивски материјал и сл.), аутор мора да достави извор одакле је преузео цитирану литературу односно може сликати или скенирати документ и послати на е-мејл: strliteratura@gmail.com.

Референце се цитирају према Ванкуверском стилу који је успоставио ICMJE (https://connect.ebsco.com/s/article/Citing-Articles-in-Vancouver-ICMJE-Style?language=en_US).

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НАКНАДЕ ЗА ОБЈАВЉИВАЊЕ ЧЛАНКА

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