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EDITORIAL
UVODNIK

GERIATRICS – STANDARDS AND THE FUTURE OF HEALTHCARE FOR THE OLDER ADULTS

GERIJATRIJA – STANDARDI I BUDUĆNOST ZDRAVSTVENE ZAŠTITE ZA STARIJE OSOBE

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Introduction

In today's society, where life expectancy is steadily increasing, geriatrics has emerged as a pivotal field of medicine dedicated to addressing the needs of older adults. This specialty offers integrated support that spans prevention, diagnosis, treatment, and rehabilitation, while respecting the physical, mental, and social dimensions of ageing. In Europe, geriatrics has evolved as a subspecialty within internal medicine, grounded in the principles of comprehensive geriatric assessment (CGA), which enables effective care and resource optimisation for the older population. While geriatrics is formally recognised in several European countries, others are still in the process of establishing and enhancing standards in both education and clinical practice.

Specific Approaches and Methods in Geriatric Medicine

At the core of geriatric practice lies the comprehensive geriatric assessment (CGA) – a multidisciplinary diagnostic process specifically tailored to the needs of older patients. CGA encompasses not only medical but also functional, psychosocial and environmental domains. The assessment team typically includes a geriatrician, nurse, physiotherapist, social worker, and psychologist, who collaborate to develop an individualised care plan. This approach is associated with improved clinical outcomes, reduced hospitalisation rates, delayed institutionalisation, and prolonged functional independence among older adults.

Professional and Educational Standards

Education and continuous professional development are critical to ensuring high-quality care in geriatrics. The European Geriatric Medicine Society (EuGMS) strives to harmonise educational standards across Europe, advocating for the inclusion of geriatrics as a mandatory subject in both undergraduate and postgraduate medical curricula. These educational initiatives aim to equip future physicians with knowledge of the physiological process of ageing, the principles of CGA, and the ethical issues uniquely relevant to geriatric medicine, such as palliative care and quality of life assessments.

Postgraduate training in geriatrics typically spans at least five years and includes both theoretical instruction and practical clinical experience in primary and acute care, geriatric psychiatry, rehabilitation, and palliative care. This comprehensive training equips professionals with the necessary skills to understand the unique challenges of the older population, and encourages a holistic approach when working with older patients.

Challenges for the Future

The future of geriatrics involves addressing several challenges. One of the most urgent is motivating young professionals to pursue a career in this field, given the growing demand for qualified geriatric personnel. Another critical need is the development of research programmes that address the specific health concerns of older adults. Geriatrics can foster interest in this specialty by promoting scientific research and

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raising public awareness of the challenges that older people face.

Moreover, the existing healthcare systems must adapt to provide longitudinal, coordinated, and proactive healthcare. This type of care requires continuous support and an integrated network of social and health services capable of effectively responding to the needs of the older population.

Conclusion

Geriatrics plays a fundamental role in improving the health and quality of life for older adults, with comprehensive assessment, multidisciplinary care, and tailored professional education making its core components. To ensure the sustainability and growth of this specialty, it is essential to increase public awareness about the importance of geriatric medicine and encourage young doctors to dedicate their professional careers to this field.

With continued investment in educational and professional standards, geriatrics will be well-positioned to meet the complex needs of the older population and contribute to the development of integrated support system that ensures long-term healthcare for older patients, improving both their health and quality of life.

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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

BONE MINERAL DENSITY IN PATIENTS WITH PSORIATIC ARTHRITIS

KOŠTANA MINERALNA GUSTINA KOD PACIJENATA SA PSORIJAZNIM ARTRITISOM

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Abstract

Introduction. Psoriatic arthritis is an inflammatory arthritis with a complex clinical presentation. The aim of this study was to assess the correlation between clinical features and bone density in patients with psoriatic arthritis, and to compare bone densitometry results with those of healthy controls. **Material and Methods.** The study included 20 patients with psoriatic arthritis and 14 healthy controls. Demographic and clinical data were collected, including nail changes and the Psoriasis Area and Severity index. All participants underwent dual-energy-X-ray absorptiometry and evaluation using the Fracture Risk Assessment Tool. **Results.** The mean age of participants was 58 ± 9.1 years, with 55% being male. Rheumatoid factor was positive in 30% of patients, nail lesions were present in 60%, and the mean Psoriasis Area and Severity Index score was 10.37 ± 10.13. A significant correlation was observed between rheumatoid factor positivity and reduced bone density (p = 0.002), as well as between nail lesions and higher fracture risk (p = 0.005). Higher psoriasis index scores were significantly associated with increased fracture risk (p = 0.03). No other statistically significant correlations were identified. Although differences were found in bone mineral density and Fracture Risk Assessment Tool scores between patients with psoriatic arthritis and controls, these did not reach statistical significance. **Conclusion.** This study demonstrated an association between reduced bone density and rheumatoid factor positivity, as well as a high fracture risk in psoriatic arthritis patients with nail lesions. These findings support the consideration of routine bone density assessment in diagnostic algorithm for psoriatic arthritis, particularly in patients with rheumatoid factor positivity and nail involvement.

Key words: Bone Density; Arthritis, Psoriatic; Osteoporosis; Psoriasis; Densitometry; Rheumatoid Factor

Sažetak

Uvod. Psorijazni artritis je zapaljenski artritis sa složenom kliničkom prezentacijom. Glavni cilj ovog rada je utvrditi korelaciju između kliničkih karakteristika i koštane gustine kod pacijenata sa psorijaznim artritisom te uporediti rezultate osteodenzitometrije između ovih pacijenata i zdravih ispitanika. **Materijali i metode.** U istraživanje je uključeno 20 pacijenata sa psorijaznim artritisom i 14 zdravih osoba. Prikupili smo demografske i kliničke podatke, kao i promene na noktima i indeks oblasti i težine psorijaze. Pacijenti su podvrgnuti dvoenergetskoj rendgenskoj apsorpciometriji i alatu za određivanje rizika od fraktura. **Rezultati.** Prosečna starost bila je 58 ± 9,1 godina, a bilo je 55% muškaraca. Pozitivan reumatski faktor imalo je 30% pacijenata, 60% je imalo promene na noktima, a prosečni indeks oblasti i težine psorijaze bio je 10,37 ± 10,13. Postojala je značajna korelacija između reumatskog faktora i smanjene gustine kostiju (p = 0,002) te zahvaćenosti noktiju i visokog rizika od preloma (p = 0,005). Indeks oblasti i težine psorijaze je bio u značajnoj korelaciji sa alatom za određivanje rizika od frakture (p = 0,03). Nije bilo drugih statistički značajnih korelacija. Postojala je razlika između gustine kosti i alata za određivanje rizika od frakture, koja nije bila statistički značajna. **Zaključak.** Ovo istraživanje pokazalo je korelaciju između gustine kostiju kod pacijenata sa psorijaznim artritisom i pozitivnim reumatskim faktorom, kao i visok rizik od preloma kod pacijenata s promenama na noktima. Stoga treba uzeti u obzir uvođenje redovnog merenja koštane gustine u dijagnostički algoritam psorijaznog artritisa, posebno kod onih pacijenata kod kojih je potvrđen pozitivan reumatski faktor i promene na noktima.

Ključne reči: gustina kosti; psorijazni artritis; osteoporoza; psorijaza; denzitometrija; reumatoidni faktor

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis with a heterogeneous clinical presentation, most often occurring in association with psoriasis. The incidence is relatively low, estimated at about 5 per 100,000 inhabitants per year, compared to rheumatoid arthritis (RA), which has an incidence of approximately 208 per 100,000 inhabitants per year [1]. Despite this, PsA often follows one of the most

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Abbreviations

BMD	– bone mineral density
DXA	– dual-energy X-ray absorptiometry
FRAX	– Fracture Risk Assessment Tool
HR	– Hazard ratio
IL	– interleukin
Ig	– immunoglobulin
NHANES	– National Health and Nutrition Examination Survey
PASI	– psoriasis area and severity index
PsA	– psoriatic arthritis
RA	– rheumatoid arthritis
RANK	– receptor activator of nuclear factor κB
RANKL	– receptor activator of nuclear factor κB ligand
RF	– rheumatoid factor
SD	– standard deviation
TBS	– trabecular bone score
TNF	– tumor necrosis factor

aggressive clinical courses among inflammatory arthritides, leading to erosions and bone destruction, features classically associated with rheumatoid arthritis (RA). For this reason, PsA has historically been underestimated in terms of its impact on bone health [2]. Over the past decade, growing attention has been directed toward bone quality in PsA and the increased frequency of fragility fractures that require prevention. Fragility fractures represent a serious clinical, social, and economic burden for patients and their families. Less than 20% of women with a hip fracture regain their pre-fracture level of functionality, while more than 40% remain unable to move independently. In addition, fracture-related mortality is significantly increased [3].

At the molecular level, the receptor activator of nuclear factor κB (RANK) and its ligand (RANKL) play a key role in maintaining the balance between osteoblast and osteoclast activity. In osteoporosis, this balance is disrupted. In PsA, RANK and RANKL expression is significantly elevated in the synovium, leading to accelerated osteoclast activation. Moreover, tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17) further promote osteoclastogenesis independently of RANKL [4].

Findings from clinical studies remain inconsistent. A German study demonstrated reduced bone mineral density (BMD) in PsA patients, with bone mass loss beginning early in the disease course [5]. In the United States, a large study involving 28,765 PsA patients reported osteopenia in 285 (0.99%), osteoporosis in 1,293 (4.5%), and fragility fractures in 176 (0.61%) patients, with statistically significant differences compared to controls ($p < 0.001$) [6]. Similarly, Frediani et al. found decreased bone density in PsA patients, accounting for age and menopausal status in women [7]. A large population-based study in the United Kingdom also showed a significantly increased risk of all fractures (Hazard ratio (HR) = 1.26) in 9,788 PsA patients. Notably, an increased fracture risk was also observed in patients with psoriasis without arthritis [8].

Conversely, two large studies reported no evidence of lower BMD or higher fracture rates in PsA patients compared to the general population [9,10].

Given these conflicting results, the aim of the present study was to investigate the correlation between clinical features and the frequency of decreased bone density in PsA patients, as well as to compare bone densitometry findings between PsA patients and healthy controls.

Material and Methods

This study included 20 patients with psoriatic arthritis (PsA) and 14 healthy control individuals. Demographic characteristics, clinical features, Psoriasis Area and Severity Index (PASI), and relevant laboratory parameters were recorded for all patients. Bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry (DXA) using a Hologic densitometer, and the risk of fracture was calculation using the Fracture Risk Assessment Tool (FRAX) [11].

Psoriasis severity was evaluated with PASI, which divides the body into four regions: head (10% of body surface area), upper extremities (20%), trunk (30%), and lower extremities (40%). For each region, erythema, desquamation and induration are scored, and these scores are summed to yield the final PASI value. Disease severity is classified as mild (<7), moderate (7–12), or severe (>12).

DXA was performed at the lumbar spine (L1–L4) and hip. T-scores, based on reference values from the National Health and Nutrition Examination Survey (NHANES) provided by the manufacturer, were used for classification. A T-score > -1.0 standard deviation (SD) was considered normal, between -1.0 and 2.5 SD indicated osteopenia, and ≥-2.5 SD indicated osteoporosis. In addition, FRAX was applied to estimate the 10-year probability of major osteoporotic fractures.

Statistical analyses were performed using SPSS version 22.0. Descriptive statistics included arithmetic mean, standard deviation, and median values. Quantitative data were expressed as absolute numbers and percentages. Categorical variables were compared using the chi-square test, while numerical variables were analyzed with either t-test or Mann-Whitney U test. Correlations between numerical variables were assessed using Pearson's or Spearman's correlation coefficients. A p-value < 0.05 was considered statistically significant.

Table 1. Features of patients and control

	Patients	Controls
Total, n	20	14
Sex (M), n (%)	11 (55)	7 (50)
Age, mean value ± SD	58±9.1	55.93±7.4
Alcohol, n (%)	1 (5)	2 (14.28)
Smoking, n (%)	4 (20%)	5 (35.71)
Glucocorticoids, n (%)	7 (35)	/
RF, n (%)	6 (30)	/
Nails, n (%)	12 (60)	/
PASI, mean value ±SD	10.37±10.13	/
Weight, mean value ±SD	76.75±15.34	73.25±11.46
BMI, mean value ±SD	26.35±3.83	26.82±2.01

BMI - body mass index; M - male; PASI - psoriasis area and severity index, RF- rheumatoid factor

Table 2. FRAX values in patients and controls

	Patients	Controls
FRAX major fracture (%, ±SD)	10.85±8.05	8.38±3.49
FRAX hip (%, ±SD)	3.71±3.24	2.48±1.30

FRAX - Fracture Risk Assessment Tool

Table 3. Correlation between clinical features, T-score and FRAX in patients with PsA

	RF	Nails	PASI	Duration of disease
L1-L4 T-score	0.03*	p>0.05	p>0.05	p>0.05
LF T-score	p>0.05	0.02*	p>0.05	p>0.05
RF T-score	0.02*	0.01*	p>0.05	p>0.05
FRAX major fracture	p>0.05	p>0.05	0.03*	p>0.05
FRAX hip	p>0.05	0.01*	p>0.05	p>0.05

FRAX - Fracture Risk Assessment Tool; L1-L4: lumbar spine 1-4; LF - left femur; PsA - psoriatic arthritis; RF - right femur
*p<0.05-statistically significant

This study was approved by the Ethics Committee of the Clinical Center, and written informed consent was obtained from all participants.

Results

The mean age of patients with PsA was 58 ± 9.1 years, while the mean age in the control group was 55.93 ± 7.4 years. In the control group, 50% of the participants were male. Both patients and controls were predominantly in the pre-obese category. Among patients, 5% reported alcohol consumption, 20% were smokers, and 35% were treated with glucocorticoids. Rheumatoid factor (RF) was positive in 30% of patients, nail involvement was present in 60%, and the mean PASI score was 10.37 ± 10.13. The mean body mass index (BMI) in the PsA group was 26.35 ± 3.83. Within this group, 9 patients (45%) had normal BMI, 7 (35%) were overweight, and 4 (20%) were obese. More detailed characteristics are presented in **Table 1**.

Although differences in bone density and FRAX scores were observed between patients and controls, these were not statistically significant ($p > 0.05$). In the PsA group, 2 patients (10%) had normal bone density, 11 (55%) had osteopenia, and 7 (35%) had osteoporosis. In the control group, 3 participants (21.42%) had normal bone density, 9 (64.29%) had osteopenia, and 2 (14.29%) had osteoporosis. These findings are illustrated in **Figures 1 and 2**, and summarized in **Table 2.**

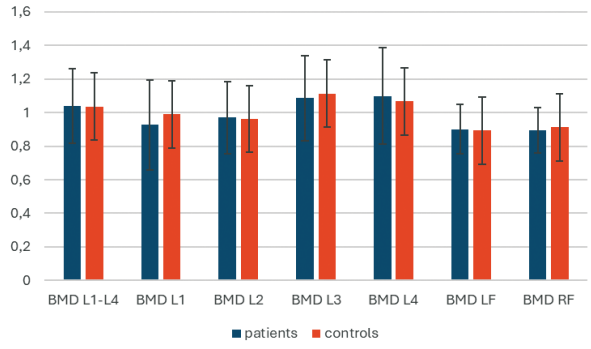

Figure 1. BMD in patients and controls The Figure shows medians with standard deviations. BMD-bone mineral density; LF-left femur; RF-right femur

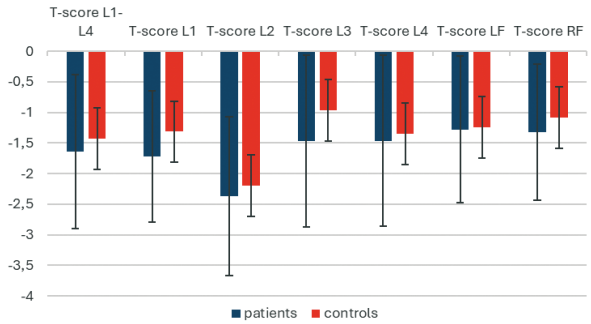

Figure 2. T-score in patients and controls The Figure shows medians with standard deviations. LF-left femur; RF-right femur group

Significant correlations were identified between RF positivity and reduced bone density of the spine and right hip ($p = 0.03$ and $p = 0.02$, respectively), as well as between nail lesions and reduced hip bone density ($p = 0.02$ and $p = 0.01$). Nail involvement was also significantly associated with higher FRAX scores ($p = 0.01$). Furthermore, a negative correlation was observed between PASI score and FRAX score for major fractures ($p = 0.03$, $r = -0.48$). Additional data are presented in **Table 3**.

Discussion

In our study, the mean age of patients was 58 ± 9.1 years, whereas previous research has reported mean ages ranging from 45.9 to 65.6 [12,13]. This variation may be attributed to differences in clinical presentation and diagnostic challenges. Gender distribution in our cohort was approximately equal, which coincides consistent with findings from other studies [13,14]. The proportion of patients consuming alcoholic or cigarettes was low, both in our study and in previous reports [12,15].

Rheumatoid factor (RF) positivity was observed in 30% of patients, with a statistically significant correlation between RF positivity and lower T-scores at the lumbar spine (L1-L4) and right hip. Although RF is primarily associated with rheumatoid arthritis (RA), it can also be detected in a proportion of healthy individuals. By binding to the Fc region of immunoglobulin (IgG), RF forms immune complexes that trigger cytokine release, inflammatory cascades, and osteoclastogenesis [16]. Our findings align with those of a Korean study, which also reported a significant correlation between RF and bone density, independent of age [17]. This supports the hypothesis that RF-mediated immune complexes promote osteoclast maturation [18].

Nail involvement was present in 60% of our patients. Previous studies have shown that PsA patients with nail lesions often experience a more aggressive disease course [19]. However, our results did not fully correspond with these findings. A possible explanation is that many of our patients were in the early disease phase and had not yet received biological therapy. Biological agents not only improve nail disease but also exert antiresorptive effect on bone [20].

We also observed a statistically significant correlation between the PASI score and FRAX for the hip. Similarly, Wang et al. reported a correlation between PASI score and bone density. This association may be explained by the cytokine-driven inflammatory cascade in active disease, which affects osteometabolism [12]. Furthermore, psoriasis itself has been linked to an increased risk fracture risk, with a hazard ratio of 2.23 (1.54–3.22) [8].

Although differences in bone density were found between PsA patients and controls, they did not reach statistically significance. A likely explanation is that we did not assess trabecular bone score (TBS), a measure that captures early microarchitectural deterioration and porosity, which may precede reductions in BMD or T-scores. Previous studies have demonstrated significant differences in TBS between PsA patients and healthy controls [5,22].

The inconsistency of results across studies may be due to variations in ethnicity or absence of biological therapy in some cohorts [6,12,21,23].

Our study has several limitations. The mostly important is the relatively small sample size, largely due to the low prevalence of PsA and the short observation period. Additionally, we did not include data on disease activity indices or menopausal status, both of which are important determinants of bone health. Future studies with larger cohorts, longer follow-up, and more comprehensive clinical data, are planned to provide more robust insights.

Conclusion

Our study demonstrated a correlation between reduced bone density and rheumatoid factor positivity in patients with psoriatic arthritis, as well as an increased fracture risk in those with nail lesions.

These findings suggest that routine bone density assessment should be considered as part of the diagnostic and monitoring algorithm for psoriatic arthritis, particularly in patients with confirmed rheumatoid factor positivity or nail involvement.

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CHARACTERISTICS OF PATIENTS WITH MYOCARDIAL INFARCTION, DIABETES MELLITUS AND CHRONIC RENAL FAILURE

KARAKTERISTIKE PACIJENATA SA INFARKTOM MIOKARDA, DIJABETESOM MELITUS I HRONIČNOM BUBREŽNOM INSUFICIJENCIJOM

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Abstract

Introduction. Patients with diabetes mellitus and acute myocardial infarction often present with multiple comorbidities, among which chronic kidney disease significantly complicates management and worsens prognosis. This study aimed to assess the impact of chronic kidney disease on clinical, echocardiographic, and coronary findings, as well as on outcomes in diabetic patients with acute myocardial infarction. **Material and Methods.** A total of 1,353 patients with diabetes mellitus and acute myocardial infarction were analyzed and stratified according to the presence or absence of chronic kidney disease. Descriptive and analytical statistical methods, including the Mann-Whitney U and χ^2 tests, were applied to evaluate demographic, clinical, echocardiographic, and angiographic parameters, treatment modalities, hospital stay, and in-hospital mortality. **Results.** Chronic kidney disease was present in 38.4% of patients, predominantly in advanced stages (III-V). Patients with chronic kidney disease were older, more often female, hypertensive, and non-smokers. Echocardiography showed lower left ventricular ejection fraction, larger left atrial volume, and impaired diastolic function. Patients with chronic kidney disease more frequently presented with non-ST elevation myocardial infarction, had multiple coronary stenoses, lower blood pressure, higher heart rates, and worse Killip class. They were less likely to undergo percutaneous coronary intervention and experienced longer hospitalization and higher in-hospital mortality. **Conclusion.** In diabetic patients with acute myocardial infarction, chronic kidney disease is associated with worse clinical, echocardiographic, and angiographic profiles, as well as poorer in-hospital outcomes. These findings underline the importance of individualized management strategies for this particularly high-risk population.

Key words: Myocardial Infarction; Diabetes Mellitus; Kidney Failure, Chronic; Renal Insufficiency; Treatment Outcome; Echocardiography; Comorbidity; Prognosis

Sažetak

Uvod. Pacijenti sa dijabetesom melitus i akutnim infarktom miokarda često imaju i druge pridružene komorbiditete, uključujući hroničnu bubrežnu bolest, što komplikuje lečenje i pogoršava prognozu. Cilj istraživanja bio je procena uticaja hronične bubrežne slabosti na kliničke, ehokardiografske i koronarografske nalaze, kao i na ishod lečenja kod pacijenata sa dijabetesom melitus i akutnim infarktom miokarda. **Materijal i metode.** U analizu je uključeno 1.353 pacijenta sa dijabetesom melitus i akutnim infarktom miokarda. Pacijenti su podeljeni u grupe, sa pridruženim hroničnim bubrežnim slabostima i bez njih. Korišćene su deskriptivne i analitičke statističke metode, uključujući Man–Vitnijev U i χ^2 test, za poređenje demografskih, kliničkih, ehokardiografskih i angiografskih parametara, modaliteta lečenja, trajanja hospitalizacije i intrahospitalne smrtnosti. **Rezultati.** Hroničnu bubrežnu slabost imalo je 38,4% pacijenata, pretežno u uznapredovalim stadijumima (III–V). Pacijenti sa hroničnom bubrežnom slabošću bili su starijeg životnog doba, češće ženskog pola, hipertenzivni i nepušači. Ehokardiografski su imali nižu ejekcionu frakciju leve komore, veći volumen leve pretkomore, kao i češće znake dijastolne disfunkcije leve komore. U navedenoj ispitivanoj grupi pacijenti su češće imali akutni infarkt miokarda bez elevacije ST segmenta, višesudovnu koronarnu bolest, niži arterijski krvni pritisak, veću srčanu frekvenciju i lošiji *Killip* status. Ređe su lečeni perkutanom koronarnom intervencijom, duže hospitalizovani i imali veću intrahospitalnu smrtnost. **Zaključak.** Pacijenti sa dijabetesom melitus, akutnim infarktom miokarda i pridruženom bubrežnom insuficijencijom imaju nepovoljnije kliničke, ehokardiografske i koronarografske nalaze, kao i lošiji intrahospitalni ishod, što ukazuje na potrebu za individualizovanim pristupom lečenju i prilagođenim terapijskim strategijama.

Ključne reči: infarkt miokarda; dijabetes melitus; hronična bolest bubrega; bubrežna insuficijencija; ishod lečenja; ehokardiografija; komorbiditet; prognoza

Introduction

Cardiovascular diseases remain the leading cause of death worldwide, with coronary artery disease – most commonly presenting as acute coronary syndrome – accounting for nearly half of all cardiovascular mortality. As life expectancy increases, clinicians are increasingly confronted with patients who not only have cardiovascular disease but also multiple comorbidities. More than 50% of patients hospitalized with acute myocardial infarction (AMI) present with at least one comorbidity, which is associated

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Abbreviations

AMI – Acute Myocardial Infarction
DM – Diabetes Mellitus
CKD – Chronic Kidney Disease
CAD – Coronary Artery Disease
PCI – Percutaneous Coronary Intervention
CABG – Coronary Artery Bypass Grafting
STEMI – ST-elevation myocardial infarction
NSTEMI – non-ST-elevation myocardial infarction

with prolonged hospitalization, higher in-hospital mortality, and more frequent readmissions [1–3].

Diabetes mellitus (DM) is a major contributor to atherosclerotic cardiovascular disease. The Framingham Study, as early as the 1970s, demonstrated that individuals with diabetes have a two- to fourfold increased risk of myocardial infarction and up to a sixfold increased risk of heart failure [4]. With the global prevalence of diabetes continuing to rise, its impact on the cardiovascular system and other organs is becoming increasingly significant. Cardiovascular complications remain the leading cause of death among diabetic patients, and post-AMI mortality is consistently higher in this group compared to non-diabetic individuals, underscoring the importance of cardiovascular risk reduction in diabetes management [5].

The coexistence of DM and chronic kidney disease (CKD) represents a growing clinical challenge, particularly in with the setting of AMI. Both conditions independently increase the risk of adverse cardiovascular outcomes, and their combined presence is frequently encountered in clinical practice. Diabetes is the leading cause of CKD in developed countries, primarily through the development of diabetic nephropathy. Conversely, CKD is strongly associated with accelerated vascular disease, systemic inflammation, and left ventricular dysfunction. As populations age and multimorbidity becomes more prevalent, understanding the interplay between DM, CKD, and AMI is crucial for optimizing patient care [6–9].

In light of these associations, the aim of this study was to compare the clinical, echocardiographic, and angiographic characteristics, as well as in-hospital outcomes, of diabetic patients with AMI, stratified by the presence or absence of CKD.

Material and Methods

From January 2016 to December 2020, a total of 1353 patients with AMI and DM were included in the study. Patients were categorized into two groups according to renal function at admission, assessed by creatinine clearance calculated using the Cockcroft–Gault formula. CKD was defined as a creatinine clearance < 60 mL/min/m², while patients with values ≥60 mL/min/m² were classified as non-CKD. Exclusion criteria were: age < 18, pregnancy, severe valvular heart disease, incomplete medical documentation or missing essential clinical data, and refusal to undergo invasive procedures such as coronary angiography or percutaneous coronary intervention (PCI). The following data were collected and analyzed: demographic and anthropometric characteristics, medical history and comorbidities, clinical parameters at admission, echocardiographic findings, coronary angiographic characteristics, treatment modality (PCI or coronary artery bypass grafting [CABG]), length of hospital stay, and in-hospital mortality.

The study protocol was approved by the local ethics committee. All procedures were conducted in accordance with Good Clinical Practice and principles of the Declaration of Helsinki.

Table 1. Risk factors in diabetes mellitus patients with and without chronic kidney disease

	Category	Non-CKD	CKD	p
Age (years)	< 65	388 (46.5%)	44 (8.5%)	< 0.001
	≥ 65	446 (53.5%)	475 (91.5%)	
Sex	Male	550 (65.9%)	234 (45.1%)	< 0.001
	Female	284 (34.1%)	285 (54.9%)	
Family history of ischemic heart disease	No	602 (72.2%)	426 (82.1%)	< 0.001
	Yes	232 (27.8%)	93 (17.9%)	
Arterial hypertension	No	119 (14.3%)	54 (10.4%)	0.038
	Yes	715 (85.7%)	465 (89.6%)	
Smoking habits	Non-smoker	459 (55.5%)	404 (77.8%)	< 0.001
	Smoker	375 (45%)	115 (22.2%)	
Dyslipidemia	No	501 (60.1%)	330 (63.6%)	0.197
	Yes	333 (39.9%)	189 (36.4%)	
BMI (kg/m²)	< 29.9	510 (61.2%)	395 (76.1%)	< 0.001
	≥ 30	324 (38.8%)	124 (23.9%)	

BMI – Body Mass Index

Table 2. Clinical findings at admission, treatment modality, and outcomes in diabetes mellitus patients with and without chronic kidney disease

	Non-CKD	CKD	p
STEMI	572 (68.6%)	315 (60.7%)	0.003
NSTEMI	262 (31.4%)	204 (39.3%)	
Systolic blood pressure (mmHg)	140.84 ± 24.01	138.31 ± 26.35	0.039
Diastolic blood pressure (mmHg)	81.76 ± 13.60	80,44 ± 14.69	0.029
Heart rate (beats/min)	83.24 ± 18.0	86.30 ± 22.09	0.012
Killip class			
I	572 (73.1%)	265 (54.1%)	< 0.001
II-IV	211 (26.9%)	225 (45.9%)	
Number of coronary artery stenoses			
Single lesion	490 (70.8%)	231 (65.6%)	0.087
More than one lesion	202 (29.2%)	121 (34.4%)	
PCI	693 (83.1%)	352 (67.8%)	< 0.001
CABG	19 (2.3%)	5 (1%)	0.075
Length of hospital stay (days)	6.18 ± 5.44	7.97 ± 6.64	< 0.001
In-hospital mortality	2 (0.2%)	16 (3.1%)	< 0.001

STEMI – ST-elevation myocardial infarction; NSTEMI – non-ST-elevation myocardial infarction; CABG – coronary artery bypass graft; PCI – percutaneous coronary intervention

Statistical analysis

Descriptive statistics were used to summarize data, including measures of central tendency, variability, and relative frequencies.

For inferential analysis, empirical distribution testing was performed. Depending on data distribution, group comparisons were made using the Mann–Whitney U test and the chi-square (χ^2) test.

Results

Based on renal function, patients were divided into two groups: those with CKD (n = 519; 38.4%) and those without CKD (n = 834; 61.6%). The mean age of the overall cohort was 68.61 ± 10.09 years, and 784 patients (57.9%) were male. Within the CKD group, advanced stages (III-V) were present in 488 patients (94%): stage III in 399 (76.9%), stage IV in 70 (13.5%), and stage V in 19 (3.7%). Significant differences in were observed in diabetes treatment modalities: insulin-dependent diabetes mellitus was more prevalent among patients with CKD (40.5%), while non-insulin-dependent diabetes was more common in those without CKD (70.1%; p < 0.001).

Risk Factors

The distribution of cardiovascular risk factors is shown in **Table 1.** Patients with CKD were more frequently older than 65 years and more often female. Compared with the non-CKD group, they had a lower prevalence of positive family history for ischemic heart disease, a higher prevalence of arterial hypertension, were more commonly non-smokers, and were less frequently obese.

Clinical, Angiographic, and Outcome Parameters

Clinical characteristics at admission, angiographic findings, treatment modalities, and in-hospital outcomes are presented in **Table 2**. Patients with CKD more frequently presented with non-ST-elevation myocardial infarction (NSTEMI) rather than ST-elevation myocardial infarction (STEMI). On admission, they had lower average systolic and diastolic blood pressure, higher heart rate, and were more often classified as Killip class II–IV, indicating more severe heart failure. Coronary angiography revealed a higher prevalence of multivessel coronary artery disease in the CKD group, suggesting more advanced atherosclerosis. Treatment strategies also differed:

Table 3. Echocardiographic parameters at admission

	Non-CKD	CKD	p
EF (%)	47.06 ± 9.25	43.21 ± 10.68	< 0.001
LAV (mL)	62.98 ± 19.99	68.10 ± 22.51	0.042
E/e'	12 ± 5	14 ± 7	<0.001
LVMI (g/m²)	76.39 ± 47.71	84.50 ± 44.08	0.238

EF – ejection fraction; LAV – left atrial volume; E/E' - early mitral inflow velocity and mitral annular early diastolic velocity ratio; LVMI – left ventricular mass index

patients without CKD were more frequently treated with PCI, whereas those with CKD were more often managed conservatively. Hospitalization was significantly longer in patients with CKD, reflecting their more complicated clinical course. Importantly, in-hospital mortality was markedly higher among CDK patients, underscoring the prognostic significance of impaired renal function in AMI.

Echocardiographic Parameters

Echocardiographic findings at admission are presented in **Table 3**. Compared with the non-CKD group, patients with CKD had significantly lower left ventricular ejection fraction, larger left atrial systolic volume, and higher E/e′ ratio.

Discussion

The interplay between coronary artery disease (CAD), DM and CKD represents a complex and multifactorial relationship with substantial clinical implications. Each condition independently increases cardiovascular risk; however, when present together, as often seen in practice, they act synergistically, accelerating disease progression, complicating treatment, and worsening prognosis. A deeper understanding of this triad is essential for optimizing management and improving patient outcomes.

In this study, the prevalence of CKD among patients with DM and AMI was 38.4%, higher than in some previous reports [10]. This may be explained by the exclusive inclusion of diabetic patients – since DM is the leading global cause of CKD – as well as by local population characteristics, as suggested in earlier research [11].

Patients with CKD were more often older than 65 years, female, hypertensive, and non-smokers, consistent with prior findings [11]. Interestingly, obesity was less common among CKD patients, possibly reflecting advanced disease stages (CKD stages III–V), where unintentional weight loss is frequent. While some studies report no significant difference in BMI between groups, discrepancies may arise from variations in CKD stage distribution [12].

Chronic kidney disease itself is a well-recognized independent risk factor for cardiovascular disease. Beyond traditional risk factors such as DM, hypertension, and dyslipidemia, CKD introduces additional pathophysiological mechanisms - including chronic inflammation, endothelial dysfunction, and oxidative stress – that promote accelerated atherosclerosis and adverse cardiac outcomes. In our study, patients with CKD more often presented with NSTEMI, lower blood pressure, higher heart rate, and Killip class II–IV, all markers of a more severe clinical condition. Angiographic findings also revealed a higher prevalence of multivessel coronary artery disease, suggesting more diffuse and complex atherosclerosis in CKD patients, consistent with prior reports [13,14].

Echocardiographic evaluation further demonstrated educed left ventricular ejection fraction, increased left atrial volume, and elevated E/e′ ratio in CKD patients. These abnormalities reflect impaired systolic and diastolic function, in line with existing literature, and represent strong predictors of adverse cardiovascular outcomes [15–17]. Such findings may partly account for the poorer prognosis in this subgroup. Treatment strategies differed notably between groups. PCI was performed less frequently in CKD patients, while conservative management was more common. This trend may reflect concerns about procedural risks such as contrast-induced nephropathy and bleeding. Nonetheless, while PCI in CKD patients is associated with higher complications and mortality rates, it remains an important therapeutic option, underscoring the need for careful risk stratification and individualized management. CKD patients in our study also had significantly longer hospitalizations and markedly in-hospital mortality, confirming the negative impact of renal impairment on clinical outcomes. These results corroborate previous evidence demonstrating that CKD is independently associated with adverse outcomes following AMI, irrespective of infarction type or treatment strategy [18].

Several limitations of this study must be acknowledged. First, its retrospective design precludes the establishment of causality between CKD and adverse outcomes in diabetic AMI patients. Second, renal function was assessed only at admission using creatinine clearance by the Cockcroft–Gault formula, without follow-up measurements. Although widely used in clinical practice, this method is less precise than eGFR estimated with MDRD or CKD-EPI equations. Due to incomplete data on serum creatinine, height, and weight, eGFR could not be calculated, and CKD classification relied solely on creatinine clearance. Similarly, left atrial volume index could not be determined because body surface area was unavailable; therefore, left atrial volume was analyzed in absolute terms. Third, information on long-term outcomes such as readmissions, recurrent cardiovascular events, or post-discharge mortality was lacking. Furthermore, important potential confounders – including medication adherence, glycemic control, and socioeconomic status – were not evaluated. Finally, as this was a single-center study, the generalizability of the findings may be limited.

Conclusion

In patients with acute myocardial infarction and diabetes mellitus, the presence of chronic kidney disease is associated with significantly worse clinical presentation and prognosis. Chronic kidney disease complicates treatment decisions, heightens procedural risks, prolongs hospitalization, and markedly increases in-hospital mortality.

Early identification of renal impairment and the application of individualized treatment strategies are crucial for improving outcomes in this high-risk population. Further research should further elucidate the mechanisms linking diabetes, chronic kidney disease, and cardiovascular disease, and support the development of tailored, multidisciplinary care approaches.

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INFECTIONS CAUSED BY GROUP B STREPTOCOCCUS AND HERPES SIMPLEX VIRUS – THE IMPORTANCE OF PREVENTION AND APPROPRIATE MANAGEMENT DURING PREGNANCY AND LABOR

INFEKCIJE IZAZVANE BAKTERIJOM STREPTOCOCCUS GRUPE B I VIRUSOM HERPES SIMPLEX – ZNAČAJ PREVENCIJE I PRAVILNOG POSTUPANJA U TRUDNOĆI I PORODAJU

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Abstract

Introduction. Group B *Streptococcus* remains one of the most significant pathogens responsible for infections during pregnancy, being closely associated with chorioamnionitis, intraamniotic infection, maternal sepsis, and neonatal morbidity. Similarly, *Herpes Simplex Virus* represents an important viral agent due to its potential to cause severe neonatal complications. The study aimed to assess postpartum women's knowledge regarding infections caused by *Streptococcus agalactiae* and *Herpes Simplex Virus*, as well as to evaluate the scope and implementation of preventive measures during pregnancy and childbirth. **Material and Methods.** This unicentric study collected data from 204 postpartum women using a structured questionnaire and medical record review. **Results**. *Group B Streptococcus* was isolated from vaginal swabs of 5.6% of participants and from urine cultures in 6.3%. In 73.33% of *Streptococcus*-positive patients, appropriate intrapartum antibiotic prophylaxis was not administered. Five women (2.45%) reported symptoms of genital herpes simplex infection during the current pregnancy, yet none underwent microbiological testing. A history of genital herpes was noted in 2.94% of participants, with only one receiving acyclovir prophylaxis to prevent symptomatic reactivation during delivery. **Conclusion**. The findings indicate a need to raise awareness among pregnant women regarding *Streptococcus agalactiae* and *herpes simplex* virus infections, and to establish a national protocol as current diagnostic and preventive practices do not align with international guidelines.

Key words: Streptococcus; Streptococcus agalactiae; Simplexvirus; Pregnancy; Delivery, Obstetric; Surveys and Questionnaires; Health Knowledge, Attitudes, Practice; Genital Diseases, Female

Sažetak

Uvod. Jedan od najznačajnijih uzročnika infekcija u trudnoći jeste bakterija *Streptococcus* grupe B koja može dovesti do horioamnionitisa, intraamnionske infekcije, sepse kod majke, kao i infekcije novorođenčeta. Bitnu ulogu u nastanku komplikacija u trudnoći imaju i virusi, od kojih infekcije izazvane virusom *Herpes simplex* tip 1 i 2 mogu ostaviti teške posledice na život ploda. Ciljevi istraživanja su bili da se utvrdi nivo znanja porodilja o infekcijama izazvanim bakterijom *Streptococcus agalactiae* virusom *Herpes simplex*, kao i da se ispita obim primene i vrsta preventivnih mera usmerenih ka navedenim infekcijama tokom trudnoće i porođaja. **Mateijal i metode.** Istraživanje je sprovedeno kao unicentrična studija. Podaci su prikupljani iz dva izvora: iz anketnog upitnika, kao i prikupljanjem podataka iz medicinske dokumentacije. **Rezultati.** U uzorku od 204 porodilje, kod 5,6% ispitanica utvrđeno je prisustvo bakterije *Streptococcus* grupe B u vaginalnom brisu, dok je kod 6,3% porodilja urinokultura bila pozitivna. Kod 73,33% pacijentkinja pozitivnih na streptokok, nije primenjena odgovarajuća intrapartalna antibiotska profilaksa. Pet (2,45%) ispitanica je primetilo simptome i znakove herpes simpleks genitalne infekcije tokom aktuelne trudnoće, međutim bris promene nije uzet ni u jednom slučaju. Od 204 porodilje, 2,94% je imalo pozitivnu istoriju obolevanja od genitalnog herpesa, a samo jedna pacijentkinja je primenjivala lek aciklovir u cilju prevencije manifestne infekcije pri porođaju. **Zaključak.** Postoji potreba za unapređenjem nivoa znanja trudnica o infekcijama izazvanim bakterijom *Streptococcus agalactiae* virusom *Herpes simplex*. Dijagnostika i prevencija pomenutih infekcija se ne sprovodi po važećim međunarodnim smernicama, zbog čega je potrebno definisati nacionalni protokol.

Ključne reči: Streptokok; Streptokokus agalaktije; simpleksvirusi; trudnoća; porođaj; ankete i upitnici; znanje o zdravlju, stavovi, praksa; polne bolesti kod žena

Introduction

Pregnancy represents a unique physiological state characterized by profound systemic adaptations designed to meet the metabolic demands of the mother and ensure proper fetal growth and development. These changes affect nearly all organ systems, including the immune system, where complex regulatory modifications occur [1,2]. To prevent maternal immune reactions against fetal alloantigens, a degree of immunological suppression is induced. However, this necessary immunosuppression simultaneously in-

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Abbreviations

GBS – Group B Streptococcus
IAP – intrapartum antibiotic prophylaxis
HSV – Herpes Simplex Virus
KIS – Clinical Information System
CDC – Centers for Disease Control and Prevention
RCOG – The Royal College of Obstetricians and Gynaecologists
BASHH – British Association for Sexual Health and HIV

creases maternal susceptibility to infections during pregnancy [3]. Globally, the prevalence of lower genital tract infections among pregnant women is estimated at 40–54% [4,5]. Such infections are major contributors to preterm birth – a complication responsible for approximately 500,000 neonatal deaths annually. *Group B Streptococcus* (GBS) alone accounts for up to 10% of all microbial causes of preterm birth [6,7].

Streptococcus agalactiae, a Gram-positive bacterium and the principle representative of GBS, remains a leading cause of neonatal morbidity and mortality worldwide [8]. This pathogen is isolated from rectovaginal swabs in approximately 10–30% of pregnant women [9]. *GBS infections* can result in a wide spectrum of complications affecting both the mother and the fetus [10]. Given its high prevalence and severe consequences, several preventive measures have been established to reduce pregnancy-related complications and neonatal infection. Intrapartum antibiotic prophylaxis, guided by antenatal screening, continues to be the cornerstone of GBS prevention and transmission control [11].

In addition to bacterial pathogens, viral infections also play a major role in prenatal morbidity [12]. Among these, Herpes Simplex Virus (HSV) is particularly significant. Although neonatal HSV infection is relatively rare – occurring in approximately 1 in 3,200 live births – it can present as localized (skin, eyes, mouth), central nervous system involvement, or disseminated infection [13]. Early identification and timely intervention are crucial to prevent vertical transmission. The consistent implementation of preventive measures against viral infections has gained increasing importance, especially in the context of global health such as pandemics, which pose additional risk to maternal and fetal well-being [12].

The aim of this study was to assess the level of knowledge among postpartum women regarding infections caused by *Streptococcus agalactiae* and *Herpes Simplex Virus*, to evaluate the extent of preventive measures undertaken during pregnancy and childbirth, and to analyze the implementation of prophylactic protocols at the Clinic of Gynecology and Obstetrics, University Clinical Centre of Vojvodina.

Material and Methods

This cross-sectional study was conducted at the Clinic of Gynecology and Obstetrics, University Clinical Centre of Vojvodina, between 4 January and 13 February 2025. The study population comprised postpartum women who delivered at term (between 37+0 and 42+6 weeks of gestation), either by vaginal delivery or cesarean section. Participation involved completing a structured questionnaire designed to assess participants' knowledge regarding infections caused by *Streptococcus agalactiae* and *Herpes Simplex Virus*. Data were obtained from two sources: (1) the questionnaire specifically developed for the purposes of this study, and (2) relevant information extracted from medical records within the Clinical Information System (KIS). Data analysis was performed using Microsoft Excel 365. Numerical variables were expressed as mean values with corresponding measures of variability, while categorical variables were presented as frequencies and percentages. Differences in the distribution of categorical variables were assessed using the chi-squared (χ^2) test. A p-value of less than 0.05 was considered statistically significant. Results are presented in tabular and graphical form. The study protocol was approved by the Ethics committee of the University Clinical Centre of Vojvodina (approval number: 00-473).

Results

A total of 204 completed questionnaires were analyzed. The chi-square test identified a statistically significant difference between primiparous and multiparous women in responses to statement 10, which addressed the efficacy of antibiotics in the treatment of *Group B Streptococcus* (GBS) infections. Participants residing in urban areas demonstrated a higher proportion of correct responses compared with those from rural settings. Statistically significant differences were also observed for statements 2, 5, 6, 13, and 20 (**Table 1).** Participants with higher education levels showed a greater proportion of correct responses across most statements. However, for statements 15, 17, and 18 – related to genital HSV infections – a higher percentage of correct responses was observed among participants with primary and secondary education. The proportion of correct responses between employed and unemployed women was comparable for most questions. A statistically significant difference was noted for statement 7, where a higher proportion of employed women (60%) correctly identified that GBS can be isolated from vaginal swabs. For statement 17, concerning neonatal HSV transmission, unemployed participants demonstrat-

Table 1. Results of the knowledge assessment regarding infections caused by *Streptococcus agalactiae* and Herpes Simplex Virus, and the importance of their prevention during pregnancy and childbirth

Parameter	True n (%)	False n (%)	Do not know n (%)
1. Infections during pregnancy may pose a risk to both the mother and the fetus.	178 (87.25)	2 (0.98)	24 (11.76)
2. Transmission of microorganisms from mother to fetus may occur throughout the entirety of gestation, as well as during labor and delivery.	148 (72.55)	8 (3.92)	48 (23.53)
3. Avoidance of direct contact with infected individuals and the use of barrier protection during sexual intercourse can prevent the transmission of viral and bacterial infections.	162 (79.41)	10 (4.90)	32 (15.69)
4. The most prevalent infections in pregnancy are bacterial infections.	130 (63.73)	10 (4.90)	64 (31.37)
5. Increased volume of vaginal discharge with a characteristic odor and discoloration, accompanied by pruritus and dyspareunia, may indicate a gynecological bacterial infection.	175 (85.78)	1 (0.49)	28 (13.73)
6. Infection with *Streptococcus agalactiae* (Group B Streptococcus) exerts a significant influence on pregnancy outcomes.	74 (36.27)	7 (3.43)	123 (60.29)
7. The presence of *Streptococcus agalactiae* (Group B Streptococcus) may be identified through microbiological analysis of a vaginal swab.	116 (56.86)	3 (1.47)	85 (41.67)
8. In neonates, *Streptococcus agalactiae* infection can result in meningitis, pneumonia, and neonatal sepsis.	50 (24.51)	4 (1.96)	150 (73.53)
9. Intrapartum administration of antibiotics significantly reduces the risk of *Streptococcus agalactiae* transmission to the neonate.	74 (36.27)	11 (5.39)	119 (58.33)
10. Antibiotic therapy is effective in the treatment of infections caused by *Streptococcus agalactiae* (Group B Streptococcus).	88 (43.14)	3 (1.47)	113 (55.39)
11. Infection with the Herpes Simplex Virus is not transmitted transplacentally from mother to fetus.	53 (25.98)	31 (15.20)	120 (58.82)
12. Herpes Simplex Virus type 2 is most commonly transmitted through sexual contact.	72 (35.29)	11 (5.39)	121 (59.31)
13. The presence of antibodies against Herpes simplex virus may be detected via the TORCH screening panel, utilized in prenatal diagnostics.	80 (39.22)	4 (1.96)	120 (58.82)
14. Genital herpes is characterized by the appearance of small vesicular lesions in the genital area, associated with pruritus, pain, and a burning sensation.	101 (49.51)	3 (1.47)	100 (49.02)
15. If a primary outbreak of genital herpes occurs within six weeks prior to delivery, the cesarean section is the recommended mode of delivery.	31 (15.20)	8 (3.92)	165 (80.88)
16. Use of acyclovir, valacyclovir, and famcyclovir has not been associated with teratogenic or harmful effects during pregnancy.	13 (6.37)	6 (2.94)	185 (90.69)
17. If a primary genital herpes infection occurs during pregnancy and active lesions are present at the time of labor, the risk of neonatal herpes infection is approximately 40%.	23 (11.27)	3 (1.47)	178 (87.25)
18. If active genital herpes lesions are present at delivery in a woman with a known history of genital herpes, the risk of vertical transmission to the fetus ranges between 0% and 3%.	15 (7.35)	8 (3.92)	181 (88.73)
19. A woman with a prior history of genital herpes before pregnancy, or the one experiencing an episode during the first or second trimester, should receive prophylactic antiviral therapy from the 36th week of gestation until delivery, in order to prevent recurrence at the time of birth.	35 (17.16)	4 (1.96)	165 (80.88)
20. If genital herpes is diagnosed in a timely manner and appropriate preventive measures are undertaken, vertical transmission from mother to neonate can be prevented in the vast majority of cases.	102 (50.00)	4 (1.96)	98 (48.04)

ed a greater proportion of correct answers (20.59%) compared with employed women (9.41%).

Overall, the assessment of knowledge regarding infections caused by *Streptococcus agalactiae* and HSV types 1 and 2, as well as their prevention, revealed that most postpartum women were inadequately informed. Among all participants, 30.88% correctly answered more than 50% of the statements, whereas 10.29% correctly answered over 70% **(Table 1)**.

Table 2 presents the proportion of participants who underwent diagnostic procedures for GBS and HSV infections. Of the 93.62% who underwent urinary analysis, 6.28% (n=12) had a positive GBS urine culture. Vaginal swabs were obtained during pregnancy in 88.2% of participants, with 5.55% (n=10) testing

Table 2. Participants' responses regarding diagnostic procedures during pregnancy

Parameter	Number (n)	%
Urine culture performed during pregnancy	191	93.62
Urine culture positive for *Streptococcus agalactiae*	12	6.28
Vaginal swab performed during pregnancy	180	88.24
Vaginal swab performed within one month prior to delivery	154	75.49
Vaginal swab positive for *Streptococcus agalactiae*	10	5.55
Vaginal swab positive for other bacteria	31	17.22
Swab taken from lesion suspected of genital herpes	0	0
TORCH test performed (IgM and IgG for HSV*)	86	42.16
Medical history taken regarding genital herpes	36	17.65

*HSV- Herpes Simplex Virus

positive for GBS and 17.22% showing other bacterial growth. Overall, 75.49% reported swab collection within one month before delivery. Notably, 36.36% of women with a positive GBS urine culture had a negative vaginal swab within four weeks prior to delivery. Five participants reported vesicular genital lesions with associated pain and burning during pregnancy; however, none underwent HSV swab testing. Serological testing for HSV antibodies was performed in 42.16% of cases, while a gynecological history regarding prior genital HSV infection was obtained in 17.65%.

Preventive measures against GBS and HSV infections implemented during pregnancy are presented in **Table 3**. All ten women with confirmed GBS colonization received treatment: five with vaginal suppositories, one with antibiotics, one with antibiotics and probiotics, and three with all three therapies. Among all participants, 40.69% reported probiotic use during pregnancy, while 41.18% used vaginal suppositories within four weeks prior to delivery. Of the 2.94% (n=6) with a history of genital herpes, only one woman (0.49%) received prophylactic acyclovir during pregnancy.

Two participants (0.98%) reported experiencing clinical manifestations of genital HSV infection for the first time during the current pregnancy. Both pregnancies were regularly monitored – one in a public healthcare facility and the other in a private institution. Both patients underwent serological testing for HSV antibodies (TORCH screening), but lesion swabs were not obtained. In one case, the gynecologist obtained a medical history regarding HSV infection.

Six patients (2.94%) reported a previous history of genital herpes before pregnancy. Among these, three experienced symptomatic infection during the current pregnancy, and two reported symptoms within six weeks before delivery. Only one patient received prophylactic acyclovir after the 36th gestational week to prevent symptomatic recurrence. A medical history concerning genital herpes was documented in two cases; however, neither received prophylactic therapy. All six women reported regular antenatal care – half in public healthcare facilities and half in private practices.

Based on the collected data, appropriate diagnostic procedures (medical history regarding HSV infection and TORCH serological) were not conducted in two of the six patients with a positive history of genital herpes **(Table 4).** Furthermore, 83.33% of those with prior HSV infection did not receive acyclovir prophylaxis before delivery. One patient, who exhibited active infection signs within six weeks before labor, did not receive antiviral treatment, thereby presenting a potential risk of vertical HSV transmission during vaginal delivery.

Analysis of clinical practices related to GBS prevention revealed the following **(Table 5)**. All 15 women with a positive vaginal or urine GBS culture received antenatal care. One-third (33.33%) were monitored exclusively in public healthcare institutions. Probiotic use during pregnancy was reported by 66.66% of GBS-

Table 3. Participants' responses regarding preventive measures during pregnancy

Parameter	Number (n)	%
Therapy was recommended in cases of positive GBS* swab	10	100
Therapy was recommended in cases of a positive swab for other pathogens	28	90.32
Probiotics were used during pregnancy	83	40.69
Vaginal suppositories were used within four weeks before delivery	84	41.18
Acyclovir was administered after 36 weeks of gestation as prophylaxis against symptomatic infection	1	0.49

*GBS - Group B Streptococcus

Table 4. Overview of missed opportunities for the diagnosis and prevention of HSV infection at the level of primary and tertiary healthcare

	Level of healthcare	Number (n)	Percentage (%)
Missed diagnosis	Primary	2/6	33.33
Missed opportunity for prophylaxis of symptomatic infection prior to delivery	Primary	5/6	83.33
Potential transmission to the neonate	Tertiary	1/6	16.67

Table 5. Summary of clinical management practices implemented in patients with confirmed *Streptococcus agalactiae* colonization

Antenatal Care	Regular	Irregular	Private healthcare	Public healthcare
Number (n)	15	0	10	5
Urine culture taken during pregnancy	Yes	No		
Number (n)	15	0		
Vaginal swab taken within one month before delivery	Yes	No		
Number (n)	13	2		
Indication for treatment	Positive urine culture	Positive vaginal swab	Both tests positive	
Number (n)	12	10	7	
Therapy recommended in case of a positive GBS* swab	Yes	No	Systemic antibiotic prior to delivery	Vaginal suppositories
Number (n)	15	0	2	5
Probiotics used during pregnancy	Yes	No		
Number (n)	10	5		
Antibiotic administered upon admission to the clinic	Yes	No		
Number (n)	4	11		

*GBS - Group B Streptococcus

Table 6. Number of patients in whom adequate preventive measures against GBS infection were not implemented

	Number (n)	Percentage (%)
Screening not performed	2	13.33
Intrapartum antibiotic prophylaxis not administered in GBS-positive patients	11	73.33
Intrapartum Antibiotic prophylaxis not administered in patients with unknown GBS status	42	84

*GBS - Group B Streptococcus

positive women. Vaginal swab within one month prior to delivery were collected in 86.66% of these cases. All patients positive for *Streptococcus agalactiae* were advised to receive specific treatment before labor onset; however, only four (26.67%) received intrapartum antibiotic prophylaxis after hospital admission, all of whom delivered by caesarean section.

A notable finding was that 13.33% of patients with urine culture positive for *Streptococcus agalactiae* had not undergone GBS screening within one month before delivery. Additionally, 73.33% of GBS-positive women, as well as 84% of those with unknown GBS status, did not receive appropriate intrapartum antibiotic prophylaxis **(Table 6).**

Discussion

Among the 204 surveyed parturients, 55% were primiparous. Overall, the proportion of correct responses was similar between primiparous and multiparous participants, except for a statistically significant difference in knowledge regarding the effectiveness of antibiotics in treating GBS infections, where multiparous women performed better. This finding may reflect knowledge gained from prior pregnancies, consistent with evidence that women colonized with GBS during their first pregnancy have a 2.2-fold higher risk of recurrence in subsequent pregnancies [14].

In the present study, postpartum women with primary and secondary education levels more frequently provided correct answers to statements related to HSV infection during pregnancy. A statistically significant difference was observed in responses concerning the transmission of genital HSV infection from mother to neonate, with unemployed participants answering correctly twice as often as employed women. Interestingly, postpartum women with lower education levels and those residing in rural areas demonstrated better knowledge regarding HSV infection, which may be attributed to greater exposure to the disease. This aligns with previous research showing a higher prevalence of infection among women of lower socioeconomic status and limited educational attainment [13,15].

Increasing awareness of the severity of these infections and the importance of preventive measures could improve adherence to prophylactic protocols and reduce disease incidence [16]. Our findings revealed that most postpartum women lacked adequate knowledge about GBS and HSV infections, which is consistent with previous studies [17,18]. Notably, 73.53% of participants were unaware that GBS can cause neonatal meningitis, pneumonia, or sepsis, while 58.33% did not know that intrapartum antibiotic prophylaxis reduces the risk of neonatal GBS infection. These results align with a larger study conducted in Saudi Arabia [17]. Additionally, only 15.2% of participants recognized the risk of vertical HSV transmission, which is considerably lower than the 27% reported by Marioka et al. [18].

A positive urine culture or vaginal swab for *Streptococcus agalactiae* during pregnancy represents a significant risk factor for neonatal infection [19]. Effective screening enables early diagnosis and timely intervention to prevent complications and vertical transmission [20,21]. The Centers for Disease Control and Prevention (CDC) recommends routine vaginal and rectal swab screening for GBS colonization between 36+0 and 37+6 weeks of gestation [22]. In our study, 75.49% of participants underwent vaginal swab testing during the final month of pregnancy; however, the exact gestational age at sampling was not recorded, which represents a methodological limitation. GBS screening coverage in our cohort was lower than that reported in France (89–96%) but comparable to Australia, where 76% of pregnant women are screened within the recommended timeframe [23,24].

Vaginal swabs were obtained from 88.2% of participants, with *Streptococcus agalactiae* was detected in 5.55%. This prevalence is markedly lower than the global average of 17.9% and the European range of 16.1–22%, as reported in a meta-analysis of 221 studies [25]. It is also lower than the 15.6% prevalence observed in a large Serbian study involving more than 5,000 pregnant women [26]. The lower rate in our sample may be attributed to the limited sample size and reliance on self-reported data rather than laboratory-confirmed results. *GBS* was identified in 6.28% of urine cultures among the 93.62% of participants who underwent testing – higher than rates reported by Petersen et al. [27]. Of note, 36.36% of women with positive urine cultures had negative vaginal swabs within four weeks of delivery. Since the presence of GBS in urine warrants intrapartum antibiotic prophylaxis regardless of swab results, microbiological urine analysis should be considered a valuable complementary diagnostic tool. Although not currently part of standard prevention protocols, these findings suggest that guideline revision may be warranted [21,22].

Genital herpes remains a prevalent sexually transmitted infection, and vertical transmission poses a serious risk of severe neonatal diseases. Therefore, timely and accurate diagnosis is crucial for prevention [13,15]. Đorđević et al. reported HSV type 2 IgG seropositivity in 12.5% of pregnant women tested in 2005 at the University Clinical Center of Vojvodina [28]. In our study, 2.45% of participants reported symptoms suggestive of genital HSV infection during pregnancy; however, no lesion swabs were obtained, contrary to current recommendations by the Joint British Association for Sexual Health and HIV (BASHH) and the Royal College of Obstetricians and Gynaecologists (RCOG). These guidelines emphasize that all suspected cases should undergo lesion sampling and receive appropriate treatment upon diagnosis [29].

Among respondents with a history of genital herpes (2.94%), only one received prophylactic acyclovir. According to current guidelines, all pregnant women with prior genital herpes should receive antiviral prophylaxis, regardless of symptom presence. Initiating acyclovir after 32 weeks' gestation significantly reduces the risk of peripartum viral reactivation, thereby lowering the likelihood of clinical manifestation and vertical transmission [29].

An analysis of the incidence of genital herpes infection among postpartum women revealed that 2.45% of participants reported symptoms suggestive of HSV infection during the current pregnancy, a rate consistent with previous published data [15]. However, none of these women underwent lesion sampling for microbiological confirmation of the diagnosis, and only one received prophylactic acyclovir therapy. This practice is inconsistent with the current recommendations of the BASHH and RCOG, which emphasize the importance of timely diagnosis through lesion swabbing and the administration of appropriate antiviral

treatment upon confirmation [29]. The observed management reflects insufficient implementation of existing diagnostic and therapeutic protocols and underscores the need to enhance both healthcare professionals' awareness and patient education regarding the importance of early identification and management of herpes simplex virus infections during pregnancy.

Evaluation of intrapartum antibiotic prophylaxis – an essential measure in preventing vertical transmission of GBS infection – revealed several concerning findings. This therapy was omitted in 73.33% of women with a positive vaginal swab or urine culture results. Particularly noteworthy is that only one-third of women with a positive urine culture for GBS received appropriate antibiotic prophylaxis during labor, despite this being a clear and absolute indication for treatment [22]. Furthermore, 84% of postpartum women with unknown GBS status did not receive intrapartum prophylaxis, despite recommendations to administer antibiotics in cases where risk factors for early neonatal infection are present. It should be noted, however, that in this study, individual risk factors among parturients with unknown GBS status were not identified, which represents a methodological limitation.

Currently, the Republic of Serbia lacks national guidelines for the prevention and management of infections caused by *Streptococcus agalactiae* and Herpes Simplex Virus. Screening and risk-based strategies are only partially implemented, and there is no active national surveillance of invasive GBS or HSV neonatal infections. The findings of this study highlight the urgent need to establish national recommendations for prevention, screening, and clinical management, as well as continuous surveillance systems. Additionally, targeted educational programs for healthcare professionals and the general population are essential to enhance perinatal care and reduce neonatal morbidity and mortality [26].

Conclusion

Based on the conducted research and the obtained findings, it can be concluded that there is a clear need to improve pregnant women's knowledge regarding infections caused by *Streptococcus agalactiae* and Herpes Simplex Virus. Approximately 25% of pregnant women are not included in Group B Streptococcus screening. Intrapartum antibiotic prophylaxis for Group B Streptococcus infection is not administered in accordance with current recommendations and clinical protocols. Similarly, the diagnosis and management of herpes simplex virus infection during pregnancy are not aligned with existing guideline standards. It is therefore imperative to establish national protocols, strengthen the motivation of healthcare professionals, and educate public awareness of the importance of preventing infections caused by Group B Streptococcus and Herpes Simplex Virus, with the ultimate goal of ensuring optimal health protection for both mother and neonate.

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OUR EXPERIENCE IN TREATING MONTEGGIA FRACTURES IN PEDIATRIC POPULATION

NAŠA ISKUSTVA U LEČENJU PRELOMA TIPA MONTEGGIA U PEDIJATRIJSKOJ POPULACIJI

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Abstract

Introduction. Monteggia fracture-dislocations in children, defined by an ulnar fracture with associated radial head dislocation, are rare, accounting for approximately 1% of pediatric upper extremity fractures. This study aimed to evaluate the characteristics and treatment outcomes of these injuries, with particular attention to the clinical relevance of the Bado classification. **Material and Methods.** A retrospective case series was conducted at the Institute for Children and Youth Healthcare of Vojvodina over a five-year period. Twenty-two patients aged ≤ 18 years with confirmed Monteggia fractures were included. Data from medical records included demographics, injury mechanisms, Bado classification, treatment method, and outcomes. Statistical analyses employed Fisher's Exact Test, Analysis of Variance, and the Mann-Whitney U test. **Results.** The study included 22 patients, with a notable incidence of Bado Type IV fractures (31.8%). Diagnostic delays were most frequent in Bado Type III (40%) and IV (28.5%) injuries. Although no statistically significant association was found between Bado type and treatment outcomes, patient age significantly influenced the choice of surgical technique (p=0.024). **Conclusion.** Patient age was a significant determinant of the treatment strategy. While the Bado classification did not demonstrate predictive value for outcomes, it remains a valuable descriptive tool. Early diagnosis and appropriate management are critical to prevent long-term complications.

Key words: Fractures, Bone; Child; Ulna Fractures; Radius Fractures; Fracture Dislocation; Fracture Fixation; Treatment Outcome

Sažetak

Uvod. Monteđa (*Monteggia)* prelomi-dislokacije kod dece, karakterisane frakturom ulne uz dislokaciju glave radijusa, retke su i čine približno 1% pedijatrijskih fraktura gornjih ekstremiteta. Studija procenjuje karakteristike i ishode lečenja ovih fraktura, procenjujući relevantnost Badoove klasifikacije. **Materijal i metode.** Sprovedena je retrospektivna analiza slučajeva na Institutu za zdravstvenu zaštitu dece i omladine Vojvodine, u trajanju od pet godina. U studiju je uključeno 22 pacijenata, uzrasta do 18 godina, sa ovim tipom preloma. Podaci su prikupljeni iz medicinskih izveštaja, fokusirajući se na demografske podatke, mehanizme povrede, Badoovu klasifikaciju, metode lečenja i ishode. Korišćeni su Fišerov egzaktni test, analiza varijanse i Man-Vitnijev U-test za statističku analizu. **Rezultati.** Uzorak je obuhvatao 22 pacijenta sa značajnom incidencijom tipa IV fraktura (31,8%). Uočeni su problemi sa dijagnostikom, posebno kod tipova III (40%) i IV (28,5%). Nije pronađena značajna povezanost između Badoovog tipa fraktura i ishoda lečenja, ali je primećena korelacija između starosti pacijenta i izbora hirurške tehnike (p = 0,024). **Zaključak.** Uzrast pacijenta bio je značajan prediktor izbora hirurške strategije. Iako prognostička vrednost Badoove klasifikacije nije statistički potvrđena u ovom uzorku, ona ostaje neophodan deskriptivni alat. Rana dijagnoza i lečenje su imperativ za sprečavanje komplikacija.

Ključne reči: prelomi kosti; dete; prelomi ulne; prelomi radijusa; dislokacija preloma; fiksacija preloma; ishod lečenja

Introduction

Monteggia fracture-dislocations in children consist of an ulnar fracture with associated radial head dislocation, disrupting both the radiocapitellar and proximal radioulnar joints [1,2]. These injuries are rare, accounting for up to 5% of all elbow fractures [3] in general population, and only about 1% of all pediatric upper extremity fractures [4,5] – in stark contrast to the supracondylar fractures, which represent up to 70% of pediatric elbow fractures [6].

First described in 1814, the injury was later classified by Bado in 1967 into four types based on the direction of radial head dislocation [7]. Type I, the most common in children, involves anterior dislocation with an apex-anterior ulnar fracture [1]. Type II, more typical for adults, features posterior dislocation and apex-posterior ulnar fracture [8]. Type III is characterized by lateral dislocation with a metaphyseal ulnar fracture, while Type IV involves fractures of both the ulna and radius with anterior dislocation of the radial head [8] **(Figure 1).**

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Abbreviations

PIN – posterior interosseous nerve
CRIM – closed reduction and immobilization
ORIF – open reduction and internal fixation
OREF – open reduction and external fixation

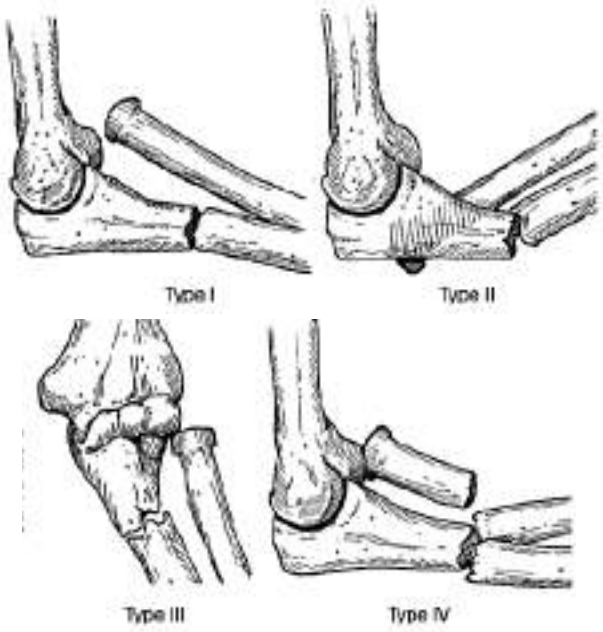

Figure 1. Aparicio Gomez A, Cadogan M. Bado classification. *Life in the Fast Lane* [Internet]. 2018 Oct [cited 2025 Oct 30]. Available from: https://litfl.com/wp-content/uploads/2018/10/Bado-Classification-of-Monteggia-Type-I-IV.png

Bado also introduced "Monteggia equivalents" for variant patterns [9], though this concept remains controversial [4,10]. Critics, such as Čepelík et al., have argued that many injuries previously termed "equivalents" – for example, those involving non-displaced proximal radius fractures – lack the same instability or treatment requirements as true Monteggia lesions and should not be classified as such [4]. While Bado Types I and III account for approximately 96% of pediatric cases [5], the injury's rarity contributes to frequent diagnostic oversight [1,5].

The Bado classification is essential for understanding the direction of instability, thereby guiding initial management. The primary treatment goal is anatomic restoration of ulnar length and alignment, which typically ensures reduction of the radiocapitellar joint [4]. However, management strategies range from conservative to surgical, depending on fracture stability [11,12]. Bado Type III fractures, in particular, are prone to failed closed treatment, with one study finding a significantly higher risk of such outcome for this type of injury [5]. Surgical fixation is indicated when stability cannot be maintained, with contemporary practice favoring early internal fixation if uncertain cases [5,11]. As Type III injuries are associated with a higher risk of complications like transient posterior interosseous nerve (PIN) palsy [4,5], the value of classification cannot be an absolute predictor of outcome.

The Letts classification introduced a pediatric-specific Monteggia equivalent – plastic deformation of the ulna with anterior radial head dislocation [14] – while Jupiter's classification expanded Bado Type II injuries into four subtypes based on the ulnar fracture morphology and associated radial head injury [8].

This study aims to analyze the relationship between Bado classification, treatment approach, and outcomes in a pediatric population.

Material and Methods

This retrospective case series was conducted at the Institute for Children and Youth Healthcare of Vojvodina in Novi Sad, a tertiary healthcare institution, covering the period, from January 1, 2019, to January 1, 2024. Ethical approval was obtained from the institutional ethics committee, and the study adhered to the principles of the Declaration of Helsinki.

Data were collected retrospectively from medical records and the hospital's electronic database ("Heliant"). A structured digital form (Google Forms) was used for data extraction and organization. Variables included demographic (age, sex), time from injury to admission and definitive treatment, injury mechanism, clinical and radiographic findings, Bado classification, treatment modality (surgical technique), hospital stay, immobilization duration, and complications. Patients aged 0-17 years, of both sexes with radiographically confirmed Monteggia fractures and complete documentation were included. Exclusion criteria were incomplete data, congenital radial head dislocation, and pathological fractures.

For analysis, patients were categorized by age (Early Childhood: 4–6 years; Middle Childhood: 7–10 years; Adolescence: 11–17 years) and mechanism of injury (fall, sports injury, traffic accident, direct blow, unknown).

Statistical analysis was conducted using IBM SPSS v25.0 (IBM Corp., Armonk, NY, USA). The significance level (alpha) was set at $p < 0.05$. Descriptive statistics were used for baseline characteristics, while Fisher's Exact Test analyzed analytical associations, ANOVA compared means across multiple groups, and the Mann-Whitney U test compared two groups.

Results

A total of 22 patients met the inclusion criteria. The basic demographic and clinical characteristics of the cohort are shown in **Table 1**. The mean age at injury

Table 1. Demographic and clinical characteristics of the analyzed cohort (N=22)

Characteristic	Number (N)	Percentage (%)
Total patients	22	100
Gender		
Male	12	54.5
Female	10	45.5
Age (years)		
Mean (SD)	8.0 (3.6)	–
Age Categories		
Early Childhood (4–6 yrs)	9	40.9
Middle Childhood (7–10 yrs)	9	40.9
Adolescence (11–16 yrs)	4	18.2
Mechanism of Injury		
Fall (low energy)	15	68.2
Sports Injury	3	13.6
Traffic Accident	1	4.5
Blow (direct trauma)	1	4.5
Unknown	2	9.1
Bado Classification		
Type I	7	31.8
Type II	3	13.6
Type III	5	22.7
Type IV	7	31.8

was 8.0 years ± 3.6 years; 12 (54.5%) were boys and 10 (45.5%) girls. The right elbow was affected in 12 (54.5%) and the left in 10 (45.5%) cased. Early and middle childhood categories were equally represented (each 40.9%). Bado types across the age categories are shown in **Table 2.** Bado Type I and Type IV were the most frequent, (each 7 cases or 31.8%), followed by Type III with 5 cases (22.7%) and Type II in 3 cases (13.6%). No statistically significant association was found between Bado type and age group (p=0.255). However, Bado Type III predominantly occurred in younger children (4 out of 5 cases, or 80%, were aged 4–6 years). The most common injury mechanism was a fall (low energy), recorded in 15 patients (68.2%), followed by sports injury in 3 patients (13.6%), traffic accidents (4.5%), and blow/direct trauma (4.5%) recorded 1 patient each, while in 2 cases the cause of injury was unknown. No statistically significant cor-

Table 2. Cross-tabulation of Bado type fracture distribution by age group (N=22)

Bado type	Early childhood (4–6 yrs)	Middle childhood (7–10 yrs)	Adolescence (11–16 yrs)	Total
Type I	1	3	3	7
Type II	1	2	0	3
Type III	4	1	0	5
Type IV	3	3	1	7
Total	9	9	4	22
Fisher's Exact Test	p=0.255			

Table 3. Association of Bado type fracture and injury mechanism (N=22)

	Fall (low energy)	Sports injury	Traffic accident	Blow (direct trauma)	Unknown	Total
Type I	4	2	0	1	0	7
Type II	2	0	0	0	1	3
Type III	4	0	0	0	1	5
Type IV	5	1	1	0	0	7
Total	15	3	1	1	2	22
Fisher's Exact Test	p=0.581					

Fisher's test did not show a statistically significant association (p=0.581).

Table 4. Distribution of operative techniques by Bado type fracture (N=21)

Bado type	CRIM	CRIF	ORIF/OREF	Total
Type I	3	1	3	7
Type II	1	1	0	2
Type III	4	1	0	5
Type IV	3	2	2	7
Total	11	5	5	21
Fisher's Exact Test	p=0.287			

*Note: One patient with Type II is missing due to unclear data on the technique.

Table 5. Average age of patients according to the applied operative technique

Operative technique	Number of patients (N)	Mean age (years)	Standard deviation (SD)
CRIM	11	6.3	2.8
CRIF	5	8.8	1.3
ORIF/OREF	5	11.8	3.8
ANOVA Test	F(2.18)=4.65	p=0.024	

relation was observed between Bado type and mechanism of injury (p=0.581) **(Table 3)**. The distribution of operative techniques by Bado fracture type is presented in **Table 4.** No statistically significant association was found between Bado type and the treatment method used. However, the minimally invasive CRIM technique predominated in Bado Type III fractures (4 out of 5 cases), while the most invasive techniques (ORIF/OREF) are most frequently applied in Types I and IV. Analysis of the average patient age for each surgical approach revealed a statistically highly significant trend (p=0.024) (**Table 5**). The least invasive technique (CRIM) was used in the youngest patients (mean age 6.3 years), whereas the most invasive method (ORIF/OREF) were employed in the oldest (mean age 11.8 years). Regarding the interval between injury and hospital admission, two Bado types stood out. Among patients with Bado Type III fractures, 40% (2 out of 5) experienced a delay in hospital admission – one was admitted four days after injury, and another after eighteen days. In the Bado Type IV group, 2 out of 7 patients (28.5%) were admitted one day after the injury, while in the Bado Type I group, one out of 7 patients (14.2%) had a one-day delay. Only patients with Bado Type II group fractures were admitted on the day of injury. Considering the time elapsed from injury to definitive management, 11 patients (50%) received treatment on the day of injury, 6 (27%) the following day, and 3 (14%) after several days. For 2 patients (9%), complete data on the exact timing of treatment were unavailable.

Discussion

Although other notable classification systems exist, such as those proposed by Letts and Jupiter [8,14], Monteggia lesions are almost universally described using the Bado classification, as it not only provides an anatomical description of the lesion but also facilitates understanding of the injury mechanism [4]. Monteggia lesions typically occur in children aged 4–10 years, often resulting from a fall on an outstretched hand [1,4]. Unlike adults, pediatric patients have open growth plates and may exhibit plastic deformation of the ulna [2]. Subtle greenstick or bowing fractures with radiocapitellar subluxation can be easily missed [15]. Acutely, these injuries impair forearm rotation and elbow stability. If untreated, chronic radial head dislocation may result in cubitus valgus, tardy ulnar neuropathy, and "mushroom" deformity of the radial head, ultimately causing functional limitation and painful radiocapitellar arthrosis [1,16].

The near-equal gender distribution in our cohort corresponds with the multicenter study by Ramski et al. [11]. The observed 31.8% incidence of Bado Type IV fractures is unusually high compared with large study of adult injuries by Weber et al. (3.1%) [17], pediatric series by Ramski et al. (4.5%) [11], and Čepelík et al., who reported a single case (<1%) in their cohort of 111 children [4]. This discrepancy may stem from the small sample size or referral bias due to our institution's tertiary status.

Prompt diagnosis requires a high index of suspicion, as any proximal ulnar fracture on plain radiographs should prompt careful evaluation of elbow alignment [8,18]. The key diagnostic feature is the loss of normal radiocapitellar alignment, where a line drawn along the radial axis must intersect the capitellum in all views [1]. This finding can be subtle, particularly in cases of plastic ulnar deformation, identifiable by the "ulnar bow sign" [1,15]. Consequently, Monteggia lesions are missed in up to 50% of cases

during the initial evaluation [15,19]. In our study, although the sample size was limited, the results partially align with these reports: 40% of patients in the Bado Type III group were diagnosed more than 24 hours after the injury, while in the Bado Type IV group, is the delay occurred in 28.5% of patients. However, due to the small cohort size, these findings should be interpreted with caution. Injuries not recognized within four weeks are considered chronic and are typically associated with functional deficits and deformity, making late reconstruction challenging and representing the most serious complication of this condition [1,16]. When diagnosed and treated promptly, pediatric Monteggia fractures generally have an excellent prognosis [5,21].

Statistical analysis of our cohort did not reveal a significant association between Bado type and any of the measured outcomes, suggesting that in this group, the Bado type itself was not a primary determinant of treatment success.

The most statistically robust finding was a strong correlation between patient age and the choice of operative technique (p=0.024). The least invasive method (CRIM) was applied in the youngest patients (mean age 6.3 years), whereas the most invasive approaches (ORIF/OREF) were used in the oldest (mean age 11.8 years). This observation is consistent with fundamental principles of pediatric orthopedic surgery, which emphasize treatment adaptation according to the bone remodeling potential [22].

This study has several limitations. The most important is the small sample size (N=22), which significantly limits statistical power. Additionally, as a tertiary referral center, our institution may treat a disproportionate number of complex cases, potentially explaining the atypical distribution of Bado types and limiting the generalizability of the findings.

Conclusion

This study provides valuable insights into the characteristics and treatment outcomes of Monteggia fractures in the pediatric population, reaffirming the clinical relevance of the Bado classification. While this classification remains the most widely used framework for describing these complex injuries, our findings suggest that it may not serve as a definitive predictor of treatment outcomes. The relatively high incidence of Bado Type IV fractures in our cohort, along with the observed diagnostic delays, underscores the persistent challenges in the timely recognition and management of Monteggia lesions. Furthermore, the significant correlation between patient age and the choice of surgical intervention highlights the importance of developmental factors in treatment planning. Despite the study's limitations – most notably the small sample size and potential referral bias – these results emphasize the need for greater awareness and early evaluation of suspected Monteggia fractures to prevent long-term complications. Future research involving larger, multicenter cohorts will be essential to further assess the influence of the Bado classification on treatment strategies and outcomes in pediatric Monteggia fractures.

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REVIEW ARTICLES
PREGLEDNI ČLANCI

LOW-GRADE SEROUS OVARIAN CANCER – WHAT IS NEW?

NISKODIFERENCIRANI SEROZNI KARCINOM JAJNIKA – KOJE SU NOVOSTI?

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Abstract

Introduction. Low-grade serous ovarian carcinoma is a distinct and relatively uncommon histologic subtype of epithelial ovarian cancer, characterized by unique biological and clinical features that differentiate from high-grade and other epithelial subtypes. **Material and Methods.** A comprehensive literature search was performed to identify interventional studies, systematic reviews, case reports, and meta-analyses published between 2010 and 2024, focusing on the diagnosis, management, and outcomes of low-grade serous ovarian carcinoma. **Diagnosis.** Ultrasound is the first-line imaging modality for evaluating ovarian and adnexal lesions. Computed tomography remains the preferred method for staging, treatment planning, and post-therapy monitoring, while magnetic resonance imaging is recommended for characterizing indeterminate adnexal masses or for evaluating extensive disease visualized on ultrasound or computed tomography. **Clinical management.** For patients with advanced–stage disease (FIGO stages II–IV), maximal cytoreductive surgery followed by six cycles of carboplatin and paclitaxel remains the standard of care. Optimal cytoreduction is associated with significantly improved overall and progression-free survival compared with suboptimal surgery. Given the intrinsic chemoresistance of low-grade serous ovarian carcinoma, primary cytoreductive surgery is generally favored over neoadjuvant chemotherapy. Emerging targeted therapies focusing on CDK4/6, MAPK, and PI3K/AKT/mTOR pathways, as well as hormonal treatments, are under investigation and have demonstrated encouraging preliminary results. **Conclusion.** The management of low-grade serous ovarian carcinoma increasingly necessitates an individualized, multidisciplinary approach. Future therapeutic strategies will likely integrate molecularly targeted and endocrine therapies with optimal cytoreductive surgery to improve outcomes for this chemoresistant and biologically distinct ovarian cancer subtype.

Key words: Ovarian Neoplasms; Carcinoma, Ovarian Epithelial; Diagnosis; Treatment Outcome; Cytoreduction Surgical Procedures; Survival; Molecular Targeted Therapy; Immunotherapy

Sažetak

Uvod. Niskodiferenciran serozni karcinom jajnika predstavlja poseban i relativno redak histološki podtip epitelijalnog karcinoma jajnika, sa biološkim i kliničkim karakteristikama koje se razlikuju od visokodiferenciranog i drugih epitelijalnih podtipova. **Materijal i metode.** Sprovedena je sveobuhvatna pretraga literature radi identifikacije interventnih studija, pregleda, studija slučaja i metaanaliza objavljenih između 2010. i 2024. godine, sa fokusom na dijagnostiku, lečenje i ishode niskodiferenciranog seroznog karcinoma jajnika. **Dijagnostika.** Ultrazvuk predstavlja prvi korak u dijagnostici ovarijalnih i adneksalnih lezija. Kompjuterizovana tomografija je preferirana metoda za određivanje stadijuma bolesti, planiranje terapije i praćenje nakon lečenja, dok se magnetna rezonanca preporučuje za karakterizaciju neodređenih adneksalnih masa ili za procenu opsežnih lezija uočenih ultrazvukom ili kompjuterizovanom tomografijom. **Kliničko lečenje.** Kod bolesnica sa uznapredovalim stadijumima II–IV prema Internacionalnom udruženju ginekologa i opstetičara, maksimalna citoreduktivna hirurgija praćena sa šest ciklusa karboplatine i paklitaksela i dalje predstavlja standard lečenja. Optimalna citoredukcija povezana je sa značajno boljim ukupnim preživljavanjem i preživljavanjem bez progresije bolesti u poređenju sa suboptimalnom hirurgijom. Primarna citoreduktivna hirurgija se generalno preferira u odnosu na neoadjuvantnu hemioterapiju zbog urođene hemioresistentnosti niskodiferenciranog seroznog karcinoma jajnika. Terapije koje ciljaju molekularne puteve, kao što su inhibitori CDK4/6, MAPK i PI3K/AKT/mTOR signalnih puteva, kao i hormonska terapija, trenutno su u fazi istraživanja i pokazuju obećavajuće preliminarne rezultate. **Zaključak.** Lečenje niskodiferenciranog seroznog karcinoma jajnika sve više zahteva individualizovan, multidisciplinaran pristup. Buduće strategije lečenja verovatno će integrisati molekularno ciljane terapije, endokrine tretmane i optimalnu citoreduktivnu hirurgiju kako bi se poboljšali ishodi kod ove hemiorezistentne i biološki specifične podvrste karcinoma jajnika.

Ključne reči: tumori jajnika; epitelijalni karcinom jajnika; dijagnoza; ishod lečenja; citoreduktivna hirurgija; preživljavanje; ciljana molekularna terapija; imunoterapija

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Abbreviations

LGSOC	– low-grade serous ovarian carcinomas
HGSOC	– high-grade serous ovarian cancer
FIGO	– International Federation of Gynecology and Obstetrics
IOTA	– International Ovarian Tumor Analysis
CT	– computed tomography
PET/CT	– positron emission tomography
MRI	– magnetic resonance imaging
LB	– lymph node
OS	– overall survival
PFS	– progression-free survival
RD	– residual disease
NACT	– neoadjuvant chemotherapy
BEV	– Bevacizumab
MAPK	– mitogen-activated protein kinase
MEK inhibitors	– mitogen-activated protein kinase (MAPK) enzymes 1 and/or 2 inhibitors
FDA	– Food and Drug Administration
FRα	– folate receptor alpha
DSS	– disease-specific survival

Introduction

Low-grade serous ovarian carcinoma (LGSOC) represents a distinct and relatively uncommon histologic subtype of epithelial ovarian cancer, accounting for approximately 3–9% of all diagnosed cases [1]. According to the MD Anderson two-tier grading system introduced in 2004, serous ovarian carcinomas are divided into high-grade and low-grade variants, which differ substantially in their molecular profiles and clinical behavior [2]. Unlike high-grade serous ovarian carcinoma (HGSOC), which predominantly affects older women, LGSOC is typically diagnosed in younger patients, with a median age of approximately 55 years. Its incidence rate remains low, ranging between 0.1 and 0.8 per 100,000 women annually [3]. Molecular and genetic analyses have demonstrated that LGSOC has a distinct pathogenesis. In contrast to HGSOC, which is strongly associated with *TP53* or *BRCA1/2* mutations, LGSOC rarely exhibits these genetic alterations. Instead, it is characterized by frequent mutations within the RAS-RAF-MAPK signaling pathway, particularly involving *KRAS*, *NRAS*, and *BRAF* genes [4,5]. These findings support the hypothesis that borderline serous tumors, which share similar molecular abnormalities, may represent precursor lesions to LGSOC. The *KRAS* G12V variant, in particular, has been associated with poorer clinical outcomes [4]. Biologically, most LGSOCs demonstrate hormone receptor positivity, with high expression of estrogen receptors (approximately 70%) and moderate expression of progesterone receptors (around 30%), providing a rationale for the use of endocrine therapy in selected patients [1,10]. Clinically, the majority of serous ovarian cancers – regardless of grade – are diagnosed in advanced FIGO stages (III or IV), accounting for approximately 85–90% of cases [1,3]. Compared with HGSOC, LGSOC typically follows a more indolent disease course, with a longer progression-free survival (PFS) (median ~90 months) and overall survival (OS) (median ~100 months) [1,3,4]. Serum CA-125 levels at diagnosis are generally lower in LGSOC than in HGSOC, which limits their diagnostic sensitivity but preserved their utility in disease monitoring [4]. Ascites is also less frequently observed at presentation [3]. Clinical symptoms are usually nonspecific and reflect the tumor's mass effect rather than its biological aggressiveness. Common presenting features include abdominal bloating, discomfort, early satiety, and, in advanced vases, urinary or respiratory symptoms related to peritoneal or pleural involvement [4]. Key clinical and biological differences between LGSOC and HGSOC are summarized in **Table 1** (*adapted from Zwimpfer, T.A.; Tal,*

Table 1. Clinico-pathological characteristics for low-grade and high-grade serous ovarian cancer

	LGSOC	HGSOC
Median age (years)	55	63
Frequency (%)	3–9%	90%
Presumed precursor	Serous borderline	STIC of fallopian tube
CA 125	Not clinical useful	Clinical useful
Positive family history	Rare	10-22%
Chemosensitivity	Rare	90%
Clinical course	Slow	Rapid
Median progression-free survival (PFS)	92	35
Median overall survival (OS)	97	72
Gene mutation reported (%)		
BRAF	5%	<1%
KRAS	19-55%	<1%
TP53	8%	>95%
BRCA	1-5%	15%

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Although the biological and clinical distinctions between LGSOC and HGSOC are well established, the first-line therapeutic approach for advanced-stage disease (FIGO II–IV) remains largely similar – maximal cytoreductive surgery followed by six cycles of adjuvant platinum-based chemotherapy, most commonly a carboplatin/paclitaxel regimen [1,10].

Material and Methods

A comprehensive literature search was conducted in the PubMed and Cochrane Central Register of Controlled Trials databases to identify studies addressing the management and clinical outcomes of women with low-grade serous ovarian carcinoma (LGSOC). The search covered publications from 2010 to 2024 and included clinical trials, meta-analyses, systematic reviews, case reports, and clinical practice guidelines. The search strategy incorporated the following key terms and their combinations: low-grade serous ovarian cancer, ovarian carcinoma, surgery, chemotherapy, and immunotherapy. The initial search retrieved over 600 records. After screening titles, abstracts, and full texts, 42 studies met the inclusion criteria, focusing specifically on the diagnosis, treatment, and outcomes of LGSOC. Among the included studies, 20 were reviews or meta-analysis, 9 clinical trials, 4 practical guidelines, 3 comparative studies, 3 retrospective analyses, 2 original research reports, and 1 multicenter study. The final selection was based on the level of clinical detail, methodological quality, and relevance to the research topic.

Diagnosis

Ultrasound represents the first-line imaging modality for the evaluation of ovarian and adnexal lesions. The International Ovarian Tumor Analysis (IOTA) group recommends the use of the Assessment of Different Neoplasias in the Adnexa (ADNEX) model, which integrates clinical and sonographic parameters to estimate the risk of malignancy [4]. According to Flicek et al. [5], the proportion of solid areas and papillary projections increases progressively from borderline tumors to LGSOC, reaching its peak in HGSOC. On ultrasound, LGSOC typically appears as a multilocular cystic lesion containing more solid elements than borderline tumors but fewer than HGSOC. The presence of echogenic calcified foci – representing psammoma bodies – is characteristic and may be accompanied by mild to moderate vascularization, as LGSOC generally exhibits lower vascularity compared with HGSOC [5,6].

Contrast-enhanced computed tomography (CT) remains the preferred imaging method for staging, treatment planning, and post-therapy surveillance of ovarian malignancies [7–9]. CT provides valuable information on lymph node involvement and peritoneal dissemination, with a reported diagnostic accuracy approaching 90% [8]. The use of oral contrast can enhance visualization in patients with low body mass index or in perimenopausal women, in whom adnexal structures may be difficult to delineate [8]. However, CT sensitivity for peritoneal disease is size-dependent and decreases markedly for implants smaller than 1 cm [7]. Typical CT findings of LGSOC include a complex cystic mass with well-defined septations, papillary projections, and solid components, which may be unilateral or bilateral [7,8,10]. The identification of calcified psammoma bodies – present in up to 90% of cases – can aid differentiation from other calcified adnexal entities such as fibromas, Brenner tumors, or teratomas [7,10–13]. Ascites is uncommon in this tumor subtype [5,7].

PET/CT has limited value in primary diagnosis due to reduced sensitivity for borderline and low-grade lesions. However, it becomes more informative in advanced disease stages or when CT findings are inconclusive. In cases of recurrent or residual disease, PET/CT shows high diagnostic performance, with reported sensitivity between 95–97% and specificity between 80–100% [7,9].

MRI is particularly recommended for characterizing indeterminate adnexal masses or for evaluating extensive lesions detected on ultrasound or CT. It provides excellent tissue contrast and demonstrated high sensitivity (approximately 83%) and specificity (84%) in distinguishing benign from malignant processes [5,7]. Malignant serous tumors usually display mixed solid and cystic morphology, irregular internal septations, and poorly defined margins [5]. The Ovarian-Adnexal Reporting and Data System (O-RADS) MRI risk stratification score has been validated in multicenter studies, providing standardized risk assessment and follow-up recommendations. Its reported sensitivity is 93% and specificity 91% for identifying malignant lesions that are indeterminate on ultrasound [14–16]. In patients with iodine contrast allergy, as well as young or pregnant women, MRI is preferred over CT. MRI is also useful for evaluating post-treatment response and excluding recurrent disease [7,8]. In women with LGSOC, peritoneal metastases often appear as foci of high signal intensity on MRI, allowing detection of even small implants, particularly in the pouch of Douglas and the left upper quadrant [6].

Clinical management

Surgery

The role of systematic lymphadenectomy in early-stage LGSOC remains controversial. Minig et al. [17] conducted a multicenter retrospective study (2000-2016) involving nine institutions across Europe and the United States, assessing the frequency of lymph node metastases and their impact on oncologic outcomes in stage I disease. All patients underwent both pelvic and para-aortic lymphadenectomy, with surgical adequacy defined as the removal of at least ten lymph nodes from each region. The study demonstrated an extremely low incidence of lymph node involvement (<1%), suggesting minimal benefit from extensive lymphadenectomy in this subgroup. These results are consistent with those of Heitz et al. [18], who reported that the likelihood of retroperitoneal lymph node metastases in epithelial ovarian cancer varies by tumor stage and histologic type. In early-stage LGSOC, lymphatic spread appears negligible, and reoperation for staging purposes should therefore be reserved tor carefully selected patients.

In advanced-stage LGSOC, optimal cytoreductive surgery remains the cornerstone of treatment. The extent of residual disease (RD) after surgery has a decisive effect on long-term survival. A retrospective analysis by Di Lorenzo et al. [2], published in 2022, including 92 FIGO stage III–IV patients treated between 1994 and 2018 demonstrated significantly longer OS in those achieving complete cytoreduction (RD <10 mm), with a median OS of 142.3 months compared to 86.4 months in patients with RD > 10 mm. PFS followed a similar pattern (38.3 vs. 23.3 months). These findings underscore that primary cytoreductive surgery achieving RD less than 10 mm markedly improves OS and PFS, whereas suboptimal debulking is associated with inferior outcomes. Therefore, maximal primary cytoreductive remains the preferred initial approach for patients with advanced LGSOC.

Chemotherapy

Platinum-based chemotherapy, typically carboplatin-paclitaxel combination administered after maximal cytoreduction, con remains the conventional standard of care for LGSOC [19,20]. Despite its widespread use, its clinical benefit is modest. Data from the Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) meta-database, which included more than 5,000 women with epithelial ovarian cancer, demonstrated markedly lower response rates in LGSOC (approximately 23%) compared with high-grade serous disease (approximately 90%) [19]. For early-stages (FIGO I–II), adjuvant chemotherapy is generally recommended, although its role in the lowest-risk categories remains debated. Specifically, adjuvant treatment may be omitted for patients with stage IA disease, while its use in stage IB/IC cases should be considered individually based on histopathologic and clinical risk factors [21]. Given the limited chemosensitivity of LGSOC, recent trials have explored targeted therapies. In 2020, Monk et al. [22] compared the MEK1/2 inhibitor binimetinib with standard single-agent chemotherapy (pegylated liposomal doxorubicin, paclitaxel, or topotecan) and found compatible median PFS (9.1 months for binimetinib vs. 10.6 months in the control arm) but with a distinct mechanism of action. A subsequent international phase II/III trial by Gershenson et al. [23], published in 2022, demonstrated a clear PFS benefit with trametinib over standard regimens (paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen) (13.0 vs. 7.2 months), establishing MEK inhibition as a promising therapeutic avenue in this chemoresistant subtype. Overall, while carboplatin–paclitaxel remains the backbone of therapy, emerging molecularly targeted options necessitate reevaluation of conventional chemotherapy paradigms.

Neoadjuvant chemotherapy (NACT)

Evidence for neoadjuvant chemotherapy in LGSOC remains limited to retrospective studies. Matsuo et al. [24] conducted a 2023 multicenter analysis of stage III–IV patients treated with multimodal therapy, demonstrating significantly inferior OS in those receiving NACT compared to primary debulking surgery (PDS) followed by adjuvant chemotherapy (4-year OS: 56.4% vs. 81%; HR 2.12; 95% CI, 1.55–2.90). Similarly, Scott et al. [25] reported only a 36% response rate to NACT, with shorter PFS relative to the PDS cohort, suggesting that early exposure to chemotherapy may delay effective cytoreduction. Alternative neoadjuvant strategies, particularly hormonal therapy, are being explored. Cobb et al. [26] reported encouraging preliminary results from a pilot trial using neoadjuvant endocrine therapies, achieving an overall response rate of almost 47%. These findings suggest that hormonal modulation may be more effective and biologically appropriate than cytotoxic regimens in this setting. Collectively, available evidence supports LGSOC's intrinsic chemoresistance and reinforces primary cytoreductive surgery as the optimal initial strategy whenever feasible. Patients with extensive or unresectable disease should undergo multidisciplinary evaluation within specialized gynecologic oncology centers [27].

Chemotherapy and bevacizumab

Bevacizumab (BEV), a monoclonal antibody against vascular endothelial growth factor (VEGF), is approved for ovarian cancer in patients at high risk of relapse (FIGO stage IV or stage III with residual disease ≥10 mm after cytoreduction) [20]. Retrospective analyses indicate that BEV, either alone or combined with chemotherapy, can induce partial and complete responses in LGSOC, both in primary and recurrent settings, with reported response rates between 47.5% and 55% [3]. The MITO 22 trial (2023) evaluated BEV in advanced LGSOC (FIGO stage III–IV), comparing combination therapy with chemotherapy alone. PFS was significantly longer in the BEV group in both first-line (47.9 vs. 22.6 months) and recurrent settings 37.1 vs. 11.2 months), suggesting a potential benefit of anti-angiogenic therapy in this population, although further prospective studies are warranted to confirm these results [28].

Hormonal therapy

Endocrine therapy has demonstrated clinical benefit in both primary and maintenance treatment for LGSOC. Approximately 70% of tumors express estrogen (ER) receptors and 30% express progesterone receptors (PR), though no clear correlation between receptor level and treatment response has been established. In a 2017 retrospective study, Gershenson et al. [29] reported a 9% objective response and 61% disease stabilization rate in patients with FIGO stage II–IV LGSOC with hormonal therapy following primary chemotherapy, with exhibited significantly longer PFS (65 vs. 26 months) compared to observation. Similarly, studies with anastrozole showed a 6-month clinical benefit rate of approximately 60% and a partial response rate of 14% [30]. Fader et al. [31] investigated the effect of hormonal monotherapy after cytoreductive surgery in stage II–IV LGSOC. Their preliminary data indicated comparable survival outcomes, with a 3-year PFS and OS of 79% for patients receiving hormonal therapy versus 92.6% for those treated with chemotherapy. These findings suggest that, in selected advanced-stage cases, hormonal therapy may represent an effective alternative to adjuvant chemotherapy. In recurrent disease, endocrine therapy alone generally yields modest response rates but can provide meaningful clinical benefit. Most clinicians advocate for maintenance hormonal therapy until disease progression or the development of unacceptable toxicity [26]. Given the molecular parallels between LGSOC and luminal breast cancer, CDK4/6 inhibitors are being explored in combination with endocrine agents. The ongoing GOG 3026 trial evaluates ribociclib plus letrozole in recurrent LGSOC, while a phase II pilot study of abemaciclib with fulvestrant in unresectable stage III–IV LGSOC, fallopian tube, or primary peritoneal carcinoma, showed a 60% objective response at ASCO 2022. The PARAGON II trial is further assessing aromatase inhibitors combined with PI3K inhibitors (alpelisib) or CDK4/6 inhibitors (ribociclib) in women with hormone receptor-positive recurrent or metastatic gynecologic malignancies. This study aims to determine whether these combinations improve overall response rates compared with historical controls from the original PARAGON trial, stratifying patients by PIK3CA mutation status. The trial is currently enrolling participants in Australia and New Zealand [30].

MEK inhibitors

Mitogen-activated protein kinase (MAPK) pathway inhibitors, specifically targeting MEK1 and MEK2, have emerged as a promising therapeutic option for patients with LGSOC. This approach is supported by frequent genomic alterations observed in LGSOC, particularly mutations in the RAS and RAF genes, including KRAS (19–55%) and BRAF (5%) [1]. The first clinical trial exploring this approach, GOG-0239, evaluated selumetinib in patients with advanced or recurrent LGSOC and reported an overall response rate of 15%, with disease stabilization in 65% of participants [32]. Subsequent investigations have examined other MEK inhibitors. Monk et al. [22] compared binimetinib with physician's choice chemotherapy and, although the trial did not meet its primary endpoint, binimetinib demonstrated notable activity, with a response rate of 16% versus 13% and a median overall survival (OS) of 25.3 months compared to 20.8 months. KRAS mutation status may serve as a predictive biomarker, guiding patient selection for MEK-targeted therapies. The phase II/III GOG-0281 trial evaluated trametinib in a similar patient population. Trametinib significantly improved PFS to 13 months compared with 7.2 months in the chemotherapy control group. Response rates were also higher with trametinib (26.2% vs. 6.2%), and median OS was extended to 37 months versus 29.2 months in the control arm [23]. Resistance mechanisms to MEK inhibitors, such as activation of phosphorylated FAK (p-FAK), have prompted the development of combination strategies. The ongoing ENGOT-ov60/NCRI/GOG-3052 phase II trial investigates a dual RAF/MEK inhibitor alone versus its combination with defactinib, a FAK inhibitor, in recurrent LGSOC, incorporating KRAS mutation status as a stratification factor [33]. Early findings suggest that MEK inhibition may meaningfully improve clinical outcomes in LGSOC, although additional trials are required to confirm efficacy and optimize patient selection.

BRAF inhibitors

Mutations in the BRAF protein, a regulating component of the MAPK pathway, are found in up to 6% of patients with LGSOC [34]. These mutations are often associated with early-stage disease and a more favorable prognosis. In 2018, Moujaber et al. [35] reported a case series of two patients harboring BRAF mutations who received BRAF inhibitors at relapse, with both achieving durable responses. Desai et al. [36] conducted a phase I, open-label trial evaluating lifirafenib, a novel reversible BRAF inhibitor, in patients with solid tumors, including one with LGSOC, demonstrating antitumor activity and an acceptable safety profile. Another BRAF-targeting agent, ABM-1310, is currently being tested in a phase I trial for locally advanced or metastatic LGSOC. Several BRAF inhibitors have already received U.S. Food and Drug Administration (FDA) approval for other melanoma, primarily metastatic melanoma, although their role in ovarian cancer remains under investigation [37].

PI3K/AKT/mTOR pathway inhibitors

Mutations in the PI3K/AKT/mTOR signaling pathway are uncommon in patients with LGSOC. However, studies have reported a considerably higher prevalence among Japanese patients (~60%) compared to Western populations (4–5.2%), suggesting possible ethnicity-related differences in pathway activation [38]. Based on these findings, Ghoneum et al. [39] investigated PI3K/AKT/mTOR inhibitors, both alone and in combination with agents targeting other signaling pathways, in patients with ovarian cancer. Metformin is of particular interest due to its inhibition of mTOR phosphorylation, thereby reducing cellular proliferation [40]. Its effect was evaluated in a retrospective control study including women with epithelial ovarian cancer, among whom those treated with metformin (for diabetes) showed significantly improved 5-year disease-specific survival (DSS) – 67% vs. 47%. In the low-grade ovarian cancer subtype, the 5-year DSS was 60% compared with 38% [41]. In 2020, Arend et al. [42] published phase II results exploring the combination of primasertib (a MEK inhibitor) and voxtalisib (a PI3K inhibitor) versus primasertib alone in patients with recurrent LGSOC. No differences in response rate were observed between the two groups. These findings highlight the need for further investigations.

Secondary cytoreductive surgery in recurrent disease

Due to the chemotherapy observed in patients with LGSOC, secondary and even tertiary cytoreductive surgeries are not uncommon. In 2022, Goldberg et al. [43] published results from a systematic review and meta-analysis demonstrating a significant improvement in OS among patients who achieved complete resection (no residual disease) during secondary cytoreductive surgery. Nevertheless, platinum-based regimens remain the standard of care for platinum-sensitive LGSOC, while non-platinum regimens, with or without bevacizumab, are preferred in platinum-resistant cases. Indications for secondary or tertiary cytoreductive surgery should be determined individually by a multidisciplinary team.

Conclusion

Since the recognition of low-grade serous ovarian carcinoma as a biologically distinct entity from high-grade serous ovarian carcinoma, understanding of its clinical behavior and therapeutic response has advanced considerably. Primary cytoreductive surgery remains the treatment of choice when complete resection is feasible, but unresectable cases and recurrent cases continue to pose major challenges due to chemoresistance. Ongoing research into hormonal, targeted, and immunotherapeutic strategies offer promising alternatives. The management of low-grade serous ovarian carcinoma increasingly requires an individualized, multidisciplinary approach, with future strategies likely to combine molecularly targeted agents, endocrine therapy, and optimal cytoreduction to improve survival outcomes in this chemoresistant and biologically distinct ovarian cancer subtype.

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PAIN ASSESSMENT IN THE MOST VULNERABLE CATEGORIES OF CHILDREN

PROCENA BOLA U NAJVULNERABILNIJIM KATEGORIJAMA DECE

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Abstract

Introduction. Medical interventions – ranging from routine venipuncture, immunizations, physical therapy, and dental procedures to invasive procedures such as lumbar puncture and bone marrow biopsy – are an essential part of pediatric health care but often cause significant pain and distress for both children and parents. In the most vulnerable groups of children (preterm and full-term newborns, preverbal infants, children with neurological and developmental disorders affecting understanding and communication, and those who are sedated for medical reasons), the subjective experience of pain cannot be adequately expressed or interpreted. **Discussion.** Pain assessment in these children represents an extremely complex clinical challenge. Evidence indicates that their well-being depends largely on the ability of healthcare professionals and caregivers to recognize signs of pain, assess its intensity, prevent complications, and initiate timely and effective pain management. **Conclusion.** Continuous education of health care professionals regarding the importance and appropriate use of pain assessment tools is essential to prevent the long-term consequences of unrecognized and inadequately treated pain, particularly in the most vulnerable pediatric populations.

Key words: Pain Measurement; Pain; Child; Infant; Infant, Premature; Children with Disabilities; Pain, Procedural

Sažetak

Uvod. Medicinske intervencije koje obuhvataju rutinsku venepunkciju, imunizaciju, fizikalnu terapiju, stomatološke zahvate, kao i invazivne procedure poput lumbalne punkcije i biopsije koštane srži, predstavljaju neizostavan deo zdravstvene zaštite dece, ali su često izvor bola i stresa, kako za decu, tako i za njihove roditelje. U posebno ranjivim kategorijama dece – prevremeno rođenim i donesenim novorođenčadima, neverbalnim odojčadima, deci sa neurološkim i razvojnim poremećajima koji utiču na razumevanje i komunikaciju, kao i deci koja su sedirana iz medicinskih razloga – subjektivno iskustvo bola ne može se adekvatno interpretirati. **Diskusija.** Procena bola u ovoj populaciji predstavlja izrazito složen klinički zadatak. Rezultati istraživanja ukazuju da deca iz najranjivijih kategorija u velikoj meri zavise od sposobnosti zdravstvenih radnika i osoba iz njihove neposredne okoline da pravovremeno prepoznaju bol, procene njegov intenzitet, spreče moguće komplikacije i primene odgovarajuće terapijske mere. **Zaključak.** Kontinuirana edukacija zdravstvenih profesionalaca o značaju i pravilnoj primeni instrumenata za procenu bola od suštinskog je značaja za prevenciju trajnih posledica koje mogu nastati kao posledica neprepoznatog i neadekvatno lečenog bola, naročito kod dece koja spadaju u najosetljivije grupe.

Ključne reči: merenje bola; bol; dete; novorođenče; prevremeno rođeno dete; deca sa posebnim potrebama; proceduralni bol

Introduction

Pain plays a protective role and is vital for survival, as it served as a warning of the limits that must be respected during activity to prevent potential tissue damage, often irreversible. The perception of pain is highly individual and differs between children and adults. A newborn adapts to acute stress resulting from painful stimuli, and this adaptation manifests through changes in endocrine, autonomic, immunological, and behavioral domains. Pain perception is influenced not only by neurophysiological mechanisms but also by psychological and environmental factors [1]. Pain prevention and management in children represent both an ethical obligation of healthcare providers and a fundamental expectation of parents within the framework of humane, comprehensive care for children. Medical interventions – ranging from routine venipuncture, immunizations, physical therapy, and dental procedures to invasive procedures such as lumbar puncture and bone marrow biopsy – are an essential part of pediatric health care, yet they are often painful and distressing for both children and parents [2]. In the most vulnerable categories of children – preterm and full-term newborns, pre-

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Abbreviations

IASP – International Association for the Study of Pain
CNS – Central Nervous System
MRI – Magnetic Resonance Imaging
AAP – American Academy of Pediatrics
CP – Cerebral Palsy
VAS – Visual Analog Scale
NRS – Numerical Rating Scales
VRS – Verbal Rating Scales
FS – face scale
PIPP – Premature Infant Pain Profile
PIPP-R – Premature Infant Pain Profile Revised
N-PASS – Neonatal Pain, Agitation and Sedation Scale
BPSN – Berne Pain Scale for Newborns
NIPS – Neonatal Infant Pain Scale
TPPPS – Toddler-Preschooler Postoperative Pain Scale
FLACC – Face Legs Activity Cry Consolability Scale
r-FLACC – Revised Face Legs Activity Cry Consolability scale
INRS – Individualized Numeric Rating Scale
PPP – Pediatric Pain Profile
NCCPC-R – Non-Communicating Children's Pain Checklist – Revised
MAPS – Multidimensional Assessment Pain Scale
EEG – electroencephalography

verbal infants, children with neurological and developmental disorders affecting understanding and communication, and those sedated for medical reasons – the subjective experience of pain cannot be adequately expressed or interpreted due to their inability to signal its presence.

Pain definition

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". Pain assessment is inherently subjective, and each individual develops a personal perception of pain based on unique experiences [3]. However, due to their inability to self-report, this IASP definition cannot be strictly applied to the most vulnerable groups of children. These children rely entirely on the ability of medical personnel and caregivers to recognize the presence of pain, assess its severity, and administer appropriate treatment.

The importance of pain assessment in children

Pain assessment is widely recognized across pediatric disciplines as both a diagnostic and therapeutic evaluation tool. It relies on the clinician's ability to observe and interpret pain within a specific clinical context. Preventing pain is not only an ethical requirement but also a medical necessity, as repeated exposure to pain can have adverse developmental and physiological effects. Misjudgment or misinterpretation of pain signals in children may lead to incorrect diagnosis, inappropriate medication dosing, or inadequate treatment, all of can result in serious consequences.

Whenever possible, the primary principle of assessment should be self-reporting. However, in the most vulnerable group of children – newborns, infants, toddlers, those with neurological or communicational limitations, or those sedated for medical reasons – meaningful self-assessment is not possible. Despite these limitations, relieving pain remains a fundamental human right [4]. Although complete elimination of pain in newborns and infants is sometimes unachievable, much can be done to minimize its duration and intensity through proper assessment and timely interventions [5].

Pain assessment in children

Multidimensional pain assessment in children is based on social communication and behavioral observation, complemented by contextual understanding, information obtained from parents or caregivers, and physiological indicators of pain [6]. Ideally, pain assessment should indicate evaluation of the following components: **Pain location**: even very young children or those with moderate disabilities can often indicate where the pain is localized. **Pain quality (nature)**: qualitative description helps differentiate the type of pain (e.g., nociceptive, neuropathic, vascular). In vulnerable children, such descriptions may be limited or absent. **Pain impact**: the degree to which pain affects daily physical and social functioning, typically reported by parents or caregivers. **Pain context**: circumstances or environmental factors influencing the perception of expression of pain. **Developmental status**: including gestational age at birth and current level of distress. **Physiological indicators**: changes in heart rate, respiratory rate, blood pressure, oxygen saturation, vagal tone, transcutaneous oxygen saturation, transcutaneous oxygen pressure, IV dioxide, palmar sweating, intracranial pressure, or plasma cortisol and catecholamine levels. **Behavioral indicators**: alternations in facial expression, body movement, crying, muscle tone, sleep patterns, and consolability. These may be absent in newborns with neurological impairment or those pharmacologically paralyzed. **Pain intensity**: beyond measuring pain levels, pain intensity serves as an indicator for selecting appropriate pain-relief measures and evaluating their effectiveness. Since, according to the IASP definition, pain assessment is subjective, its application in individuals unable to self-assess remains a particular challenge, especially in vulnerable pediatric population.

Characteristics of pain assessment in children from vulnerable categories

Fetal pain. For human to experience pain, a set of physiologically mature neurological structures is required. Additionally, the experience to pain and its differentiation as such depend on higher cognitive processes related to consciousness and memory [7]. The de-

velopment of neural pathways involved in the pathophysiology of pain begins early in fetal life – around the seventh week of gestation – with subsequent formation of the thalamus and cortical neural pathways. Some authors suggest that pain does not occur before 24 weeks of gestation, since the central nervous system (CNS) structures necessary for pain perception – such as the cortex, spinal cord, and thalamus – are not yet fully developed [8]. Others argue that pain perception may begin between the 12th and the 20th week of gestation, mediated by developing neural structures. Behavioral changes associated with pain, such as simple motor responses, crying, and facial expressions, have been described in fetuses and preterm newborns [9]. Several physiological reactions – such as crying, withdrawal movements, and changes in stress hormone levels – can be interpreted as potential indicators of fetal pain. Magnetic resonance imaging (MRI) and magnetoencephalographic studies have demonstrated fetal reactions to vibroacoustic and visual stimuli in the third trimester. Ultrasound has provided insight into fetal behavior, including crying, acute pain expressions during surgery, and movement responses to contact with an amniocentesis needle. Fetuses exposed to prolonged and painful invasive procedures exhibit elevated plasma concentrations of cortisol and β-endorphins [10].

Newborns, infants and toddlers. MRI studies in newborns exposed to painful stimuli have demonstrated activation of brain regions responsible for coding sensory and affective components of pain, similar to those in adults. Excessive or prolonged exposure to pain in early life can be harmful, resulting in adverse physiological effects and long-term neurodevelopmental consequences. Preterm infants who experience repeated painful interventions often develop hyperalgesia and allodynia due to prolonged stress. Very preterm infants (<32 weeks of gestation), who undergo numerous painful procedures during a critical period for cerebral vulnerability, require special attention. Repeated exposure to pain in these infants has been associated with alternations in brain development, cortical thinning, white matter microstructural changes, and impaired functional cortical activity, which may result in cognitive deficits later in childhood [11]. Children experience pain differently from adults. The American Academy of Pediatrics (AAP) and the American Pain Society define pediatric pain as "a concept of pain and suffering that extends far beyond the immediate physical sensation, encompassing emotional, cognitive, and behavioral components, as well as developmental, environmental, and sociocultural factors". This definition underscores the subjective nature of pain and the role of fear and anxiety, particularly separation anxiety, in amplifying pain perception. An important goal of pediatric pain management is to eliminate the pain associated suffering.

Children with neurological impairment. Neurological disorders in children – progressive or non-progressive, such as cerebral palsy (CP) – often affect posture and movement and are frequently accompanied by pain of varying origin, localization, intensity and duration. This pain significantly compromises the quality of life of affected children and their caregivers. According to the existing literature, pain negatively impacts the quality of life in 27–75% of children with CP. Approximately 25% experience moderate to severe pain, and multiple pain sources are present in over 12% of cases. Pain in children with neurological impairment can arise from musculoskeletal deformities, hip dislocation or subluxation, hypertonia, dystonia, constipation, surgical intervention, or contractures [12]. Headaches are also common in these children, often resulting from muscular weakness, increased tone, or abnormal postures of the head and neck, leading to sleep disturbances and further reducing participation in daily activities such as play and learning. Abdominal pain may be caused by medication side effects, feeding difficulties (e.g., poor coordination of chewing and swallowing, gastroesophageal reflux, slow bowel passage, or constipation – particularly in children who remain seated for extended periods and cannot independently change position. Due to their limited ability to communicate, understanding of the cause and severity of pain in non-verbal children with neurological disorders is often challenging. Valuable information can be obtained from parents or caregivers [13]. Existing unidimensional and multidimensional pain assessment scales and questionnaires developed for newborns, children, and adolescents are not equally applicable to the assessment of chronic pain in children with severe cognitive and motor deficits.

Sedated, critically ill, or physically restrained children. For most children admitted to pediatric intensive care units, the use of standard pain assessment scales is often not feasible, as many of these patients are sedated, intubated, or otherwise unable to communicate. The same limitation applies to children under three years of age who are still in the preverbal phase of development. In such cases, pain recognition relies on specialized assessment tools that evaluate physiological changes, facial expressions, or motor responses to pain.

Tools for pain assessment in children

Clinical scales adapted to the child's age represent the most commonly used instruments for pain assessment and monitoring [14]. These scales are designed either for self-reporting or for observer-based

assessment, when the evaluation relies on behavioral and physiological indicators of pain.

In preverbal children (1 Month to 3 Years), pain assessment primarily depends on the observation of facial expressions, motor activity, and physiological reactions such as crying. In the verbal phase (3-8 Years), self-assessment becomes possible through visual aids such as photographs or drawings of faces. From the age of 8, children are generally capable of reliably self-reporting their pain intensity. Several standardized tools are commonly employed in clinical practice:

Visual analog scale (**VAS**): A 10 cm horizontal line with endpoints labeled "No pain" (0) and "Worst imaginable pain" (10). The child marks the point on the line corresponding to their subjective level of pain. Scores are interpreted as follows: VAS < 4 indicates mild to moderate pain, 4-6 indicates moderately severe pain, and >6 indicates severe pain.

– **Categorical Numerical Rating Scales** (**NRS**): children express the perceived intensity of pain on a numerical scale ranging from 0 (no pain) to 10 (the worst imaginable pain)

– **Categorical Verbal Rating Scales** (**VRS**)**:** Patients select or verbalize the word that best describes their pain intensity.

– **Graphic scales** may use drawings of faces (Face scale – **FS**) varying from happy to sad depending on the level of pain, color ranges, columns, or thermometers filled to a lesser or greater degree, etc.

Tools for pain assessment in children unable to self-assess pain intensity

The following instruments are primarily designed to evaluate facial expression, crying or vocalization, body posture, muscle tone, and movement, in accordance with the child's maturity, age, sensory capacity, cognitive status, and functional abilities.

Newborns, infants and toddlers (Table 1) [15]

– Premature Infant Pain Profile (**PIPP**): adapted to preterm infants

– Premature Infant Pain Profile Revised (**PIPP-R**): adapted to preterm infants

– Neonatal Pain, Agitation and Sedation Scale (**N-PASS**): adapted to preterm infants

– Berne Pain Scale for Newborns (**BPSN**): adapted to preterm infants

– Neonatal Infant Pain Scale (**NIPS**) (includes measures of heart rate and oxygen saturation).

– Toddler-Preschooler Postoperative Pain Scale (**TPPPS**).

– Face, Legs, Activity, Cry, Consolability Scale (**FLACC**).

Children with neurological impairment

– Revised Face, Legs, Activity, Cry, Consolability scale (**r-FLACC**): Enables caregivers to add behavioral descriptors that reflect a specific child's unique pain manifestations **(Table 2)** [15].

– Individualized Numeric Rating Scale (**INRS**): Combines a standard 0-10 numerical scale with caregiver-provided behavioral expressions of pain-related reactions.

Table 1. Neonatal pain scales

Pain scale	Gestational age	Parameters	Type of pain	Metric scales
PIPP-R (revised pain profile for preterm infants)	26 weeks to full-term	Heart rate and oxygen saturation, wakefulness, browridge prominence, eyestrain and nasolabial fold	Procedural and postoperative	0–21
CRYING (cries, requires oxygen, increased vital signs, facial expression, insomnia)	32-56 weeks	Blood pressure, heart rate, oxygen saturation. Crying, facial expression, insomnia	Postoperative	0–10
NIPS (newborn infants pain scale)	28-38 weeks	Respiration pattern. Facial expression, crying, arms, legs and wakefulness.	Procedural	0–7
COMFORT neo	24-42 weeks	Respiratory response, blood pressure, cardiac action, wakefulness, anxiety, physical movement, muscle tone and facial strain.	Prolonged	8–40
NFCS (neonatal face coding system)	25 weeks to full-term	Browridge prominence, eyestrain, nasolabial fold, open lips, stretched mouth, labial pouch, tense tongue, chin shivering	Procedural	0–10
N-PASS (neonatal pain, agitation and sedation scale)	0–100 days	Heart rate, respiration rate, blood pressure and oxygen saturation. Crying or irritability, behavioral state, facial expression, extremities and tone	Acute and prolonged pain, also assesses sedation	Pain 0–10 Sedation 10–0
EDIN (echelle de la douleur inconfort noveau-ne)	25-36 weeks	Facial activity, bodily movement, sleep quality, quality of contact with nurses and consolability	Prolonged	0–15
BPSN (Bern pain scale for newborns)	27-41 weeks	Respiratory pattern, heart rate and oxygen saturation. Wakefulness, crying duration, time to console, skin color, browridge prominence with eyestrain and posture	Procedural	0–27

Table 2. Face, Legs, Activity, Cry, Consolability Scale – FLACC

	0	1	2
Face	No particular expression or smile.	Occasional grimacing or frowning, withdrawn, uninterested.	Frequent to constant chin shivering, clenched jaws.
Legs	Normal or relaxed position.	Restless, tense.	Kicking or elevated legs.
Activity	Cries softly, normal sensations, moves easily.	Wiggling, forward-backward motion, tense.	Arching, stiff or twitching.
Cry	No crying, awake or asleep.	Moaning or wining; occasional complaints.	Constant crying, screaming or sobbing, frequent complaints.
Consolability	Content, relaxed.	Consoled by occasional holding, hugging or conversation .	Hard to console.

Table 3. Multidimensional Assessment Pain Scale

	0	1	2
Vital signs: heart rate and/or blood pressure	Within baseline	Increase by 10 or more heart beats per minute and/or increase in BP by more than mmHg.	Decrease by 10 or more heart beats per minute and/or decrease in BP by more than 10 mmHg.
Respiration pattern	No change	Onset or increase of respiratory distress.	Severe respiratory distress
Facial expression	Relaxed	Grimace	Grimace accompanied by soft or faint crying
Bodily movements	No movements or purposeful action.	Restless	Stiff and/or limited bodily movements.
State of excitement	Calm or asleep	Hyperactive	Rule out

No pain, 0; mild pain, 1–2; moderate pain, 3–5; strong pain, 6–8; extreme – maximal pain, 9–10.

– Pediatric Pain Profile (**PPP**): A behavioral checklist assessing both physical observation and functional changes (e.g., refusal to eat, disturbed sleep).

– Non-Communicating Children's Pain Checklist – Revised (**NCCPC-R)**: Comprehensive tool listing behaviors for assessing pain in children aged 3-18 years with cognitive or communication impairments.

Sedated, critically ill or physically restrained children

– COMFORT Scale: Assesses nine parameters, each rated 1-5, yielding a total score from 9 to 45. It includes heart rate and blood pressure assessment.

– **COMFORT-Behavior** (COMFORT-B): It includes assessment of the level of sedation, and excludes physiologic elements.

– Face, Legs, Activity, Cry, Consolability (**FLACC) Scale**: Evaluates five behavioral domains (facial expression, leg posture, spontaneous activity, characteristics of crying and consolability), each scored from 0 to 2; total scores range from 0 (no pain) to 9-10 (intolerable pain).

– Multidimensional Assessment Pain Scale (**MAPS)**: Observes body movements and facial expression, complemented by physiologic measures such as respiration, heart rate, and blood pressure. Similar to the FLACC scale, pain intensity is scored from 0 (no pain) to 9-10 (intolerable pain) **(Table 3)** [15].

Discussion

Observational pain scales do not always allow differentiation between pain-induced distress and distress of a different origin, such as physiological instability or fear. Physiological parameters (e.g., heart rate, oxygen saturation) vary in response to pain but are less specific and reliable indicators compared to behavioral observation. Therefore, therapeutic decisions should be based on all aspects of assessment and potential sources of distress, including physiological, developmental, and psychosocial factors. The use of "pain score cut-points" for determining pain intensity is often inadequate for guiding medical treatment, as it may lead to both over- and under-medication. Instead, changes in pain intensity scores, observation of pain-related behaviors, treatment response, and overall child functioning should be evaluated concurrently when making treatment decisions. Recent studies have demonstrated that behavioral responses – such as facial grimacing, withdrawal reflexes, and crying – correlate more strongly with nociceptive cortical activation than physiological changes alone, thereby improving diagnostic accuracy in preverbal children. Consequently, multidimensional pain assessment scales that integrate behavioral, physiological, and contextual indicators are increasingly recommended in neonatal and pediatric pain assessment guidelines [2]. Simple clinical observa-

tions, such as the return of appetite, resumption of routine activities, social interactions, and sleep patterns, can be assessed easily through interviews with parents or direct observation. Critically ill patients, however, often cannot express pain or display immediate behavioral changes. In pediatric intensive care settings, pain responses may be masked by sedation, neuromuscular blockade, or critical illness-related encephalopathy. The use of newer tools such as the COMFORT-B scale and individualized behavioral descriptors (e.g., r-FLACC) has improved the detection of pain in children with limited communication abilities [3,4]. There remain substantial gaps in healthcare professionals' education regarding pediatric pain management, underscoring the need for more comprehensive and continuous training. Evidence from interprofessional education programs (e.g., Project ECHO® for Pediatric Pain) indicates that structured, continuing education improves pain assessment accuracy and reduces iatrogenic undertreatment of pain. Moreover, parental involvement and shared decision-making enhance clinical outcomes and minimize both overestimation and underestimation of pain [5–7]. Despite growing awareness, pain continues to be undertreated in vulnerable pediatric groups. Recent research highlights the potential of artificial intelligence-supported monitoring systems and novel biomarkers – such as heart rate variability, EEG-based cortical activation patterns, and salivary cortisol – to complement traditional scoring systems and enable early detection of distress in infants and neurologicall y impaired children.

Conclusion

No single indicator can perfectly reflect pain. Pediatric pain represents a complex clinical challenge that requires a multimodal and individualized management approach. Continuous, adaptable education and mentorship in pediatric pain assessment are essential for healthcare professionals. The clinical strategies summarized in this paper can help improve pain recognition and management in the most vulnerable pediatric populations. Research in this field is relatively recent, both globally and within our country. Further development of assessment tools based on physiological, behavioral, hormonal, and endocrine indicators is necessary to deepen understanding of pain perception in these groups. Until such tools are widely available, combining thorough anamnesis, behavior and physiological observation, patient history, physical examination, laboratory findings and, contextual clinical judgment remains an indispensible component of effective pediatric pain assessment and management – a practice that continues to balance science with clinical artistry.

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CASE REPORTS
PRIKAZI SLUČAJEVA

OVARIAN TORSION – A LOW INCIDENCE DISEASE OFTEN LEADING TO AVOIDABLE OVARY LOSS

OVARIJALNA TORZIJA – RETKO OBOLJENJE KOJE ČESTO DOVODI DO NEPOTREBOG GUBITKA JAJNIKA

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Case report
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Abstract

Introduction. Ovarian torsion is an acute gynecological condition that can occur at any stage of a woman's life - from the fetal and neonatal period, through premenarche, reproductive age, and into postmenopause. The highest incidence of torsions is observed during the reproductive period. The most common risk factors include the presence of an adnexal mass (such as a functional ovarian cyst or a benign tumor), enlarged ovaries due to polycystic ovary syndrome or ovarian hyperstimulation, and a history of previous surgical interventions. Torsion results from partial or complete rotation of the adnexal structures, leading to partial or complete obstruction of blood flow and the onset of symptoms such as abdominal pain, nausea, and vomiting. **Case report.** This paper presents four cases of ovarian torsion during the reproductive period, all caused by benign conditions. The first case involved strangulation of the ovarian pedicle around postoperative adhesions. The second case described adnexal torsion with tubal rupture, resulting in pelvic hemorrhage and localized peritonitis. The third case showed incomplete torsion of the ovary with a functional ovarian cyst and the development of adhesions. The final case involved a torsed benign ovarian tumor – fibrothecoma. **Conclusion.** Although ovarian torsion is occurrence relatively rare condition, it is typically associated with benign causes and can present as acute abdomen requiring emergency surgical intervention. Prompt diagnosis is crucial for preserving ovarian function, preventing complications, and safeguarding fertility.

Key words: Ovarian Torsion; Abdomen, Acute; Ovarian Cysts; Ovarian Neoplasms; Signs and Symptoms; Early Diagnosis; Treatment Outcome

Sažetak

Uvod. Ovarijalna torzija predstavlja akutno stanje u ginekologiji i može se javiti, u svim periodima života žene od fetusa i neonatusa, devojčica u premenarhi, kod žena u reproduktivnom periodu i kod žena u postmenopauzi. Najveći broj torzija dešava se u reproduktivnom periodu, a najčešći faktori rizika su prisustvo adneksalne mase – funkcionalne ovarijalne ciste ili benignog tumora ili prisustvo uvećanih jajnika kod sindroma policističnih jajnika ili ovarijalne hiperstimulacije i kod žena sa anamnezom prethodnih hirurških intervencija. Torzija nastaje usled parcijalne ili kompletne rotacije adneksalnih potpornih struktura rezultirajući parcijalnom ili kompletnom opstrukcijom krvotoka i posledičnim simptomima – abdominalna bol, mučnina, povraćanje. **Prikaz slučaja.** U ovom radu prikazani su različiti uzroci benigne prirode koji mogu dovesti do torzije jajnika u reproduktivnom periodu života žene. U prvom slučaju prikazana je strangulacija ovarijalne peteljke oko priraslica nakon hirurške intervencije. U drugom slučaju radi se o torziji sa rupturom tube koja je prouzrokovala krvarenje u maloj karlici i razvoj lokalizovanog peritonitisa. U trećem slučaju prikazana je nepotpuna torkvacija jajnika sa funkcionalnom ovarijalnom cistom i stvaranjem priraslica. U poslednjem slučaju opisan je torkvirani benigni tumor – fibrotekom jajnika. **Zaključak.** Iako je ovarijalna torzija retko stanje i u najvećem broju slučajeva benigne patologije, može dovesti do razvoja akutnog abdomena koji zahteva urgentno hirurško lečenje. Pravovremeno postavljanje dijagnoze je važno kako za očuvanje funkcije jajnika tako i za prevenciju komplikacija i očuvanja fertiliteta.

Ključne reči: torzija jajnika; akutni abdomen; ovarijalna cista; tumori jajnika; znaci i simptomi; rana dijagnoza; ishod lečenja

Introduction

Ovarian torsion is an acute gynecological condition that can occur at any age, from neonates and premenarchal girls to women of reproductive age and postmenopausal women [1]. The majority of cases occur during the reproductive period [2]. Although the true incidence remains unknown, ovarian torsion is estimated to account for 2.7-4% of all gynecological surgical emergencies, making it the fifth most com-

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Abbreviations

HCG – human chorionic gonadotropin
CRP – C-reactive protein
CA – cancer antigen

mon indication for urgent gynecologic surgery [3]. Torsion results from the partial or complete rotation of the adnexal structures, typically the ovary and fallopian tube, around the infundibulopelvic and utero-ovarian ligaments. The rotation leads to a reduction or complete cessation of blood flow to the ovary, causing ovarian enlargement due to edema, ischemia, necrosis, or local hemorrhage, and may ultimately result in loss of ovarian function [1,4,5]. The severity of clinical symptoms and morphological changes depends on the degree and duration of vascular compromise. In most cases, both the ovary and fallopian tube are involved in the torsion. Isolated torsion of either the ovary or the tube is rare and typically referred to as partial torsion. Uncommon presentations include bilateral and asynchronous ovarian torsion, which have also been reported in the literature [6]. The most significant risk factors for ovarian torsion in reproductive-age women include the presence of adnexal masses (functional cysts or benign tumors), enlarged ovaries in polycystic ovary syndrome (as defined by the Rotterdam criteria) [7], ovarian hyperstimulation syndrome, previous ovarian torsion [8], and prior pelvic surgery resulting in adhesions. Prompt diagnosis is essential to preserve ovarian function and prevent complications [9].

Aim of this paper is to present a series of ovarian torsion cases caused by benign etiologies reproductive–aged women, diagnosed and treated at a secondary-level hospital. All procedures involving human participants were conducted in accordance with the ethical standards of 1964 Helsinki Declaration and its subsequent amendments, and were approved by the Ethics Committee of the General Hospital Pirot. Written informed consent was obtained from all patients for publication of the presented material.

Case Reports

Case 1

A 46-year-old woman was referred to the General Hospital Pirot with complaints of intermittent abdominal pain that had begun earlier the same day, accompanied by vomiting and diaphoresis. Her medical history included an appendectomy 25 years prior and a videolaparoscopy for a right-sided ectopic pregnancy 18 earlier. She had previously been diagnosed with a myoma and reported two vaginal deliveries. Her last menstrual period had begun three days prior to presentation. On admission, is the patient was afebrile with a body temperature of 36.4 °C, normotensive (BP 120/65 mmHg), with a heart rate of 60 bpm and arterial oxygen saturation of 95%. Laboratory workup, including serum human chorionic gonadotropin (hCG) and C-reactive protein (CRP), was initiated. Abdominal plain radiography and ultrasound were also performed. Physical examination revealed a rigid and tender abdomen with diffuse guarding. Speculum examination showed minor bleeding from the cervix os. Bimanual examination revealed a positive Proust sign, a tender and immobile uterus, and bilateral adnexal tenderness, more pronounced on the right. The Douglas pouch was tender and filled. Transvaginal ultrasound demonstrated a retroverted, retroflexed uterus measuring 70.6 x 69.6 mm, with a posterior wall myoma measuring 4 cm in diameter. The left ovary appeared normal, containing small follicles, and measured 30.9 x 25 x 2 mm. The right ovary was located posterior to the uterus and was enlarged, measuring 80.3 x 37.8 mm. It contained a 40 mm cyst with mixed echogenicity, as well as two smaller cysts. Color Doppler showed no detectable blood flow in the right ovary, and a small amount of fluid around it. The patient was taken to urgent surgery, where intraoperative findings revealed a torsed, cystic, and enlarged right ovary located in the Douglas pouch, surrounded by adhesions and displaying dark discoloration. Following adhesiolysis, a right oophorectomy was performed. Histopathological analysis confirmed hemorrhagic infarction of the right ovary. The patient recovered with no complications, and was discharged on postoperative day five.

Case 2

A 40-year-old woman presented to the Gynecology Department with severe pelvic pain that had begun five days earlier. Although her menstrual cycles were regular, she experienced an episode of intermenstrual bleeding on the day of admission, accompanied by an intensification of pain. Upon presentation, the patient was conscious, orientated, afebrile and normotensive. Speculum examination revealed minor ex utero bleeding. Bimanual examination demonstrated a tender and filled tender Douglas pouch, with mild tenderness in the left adnexal region and pronounced tenderness on the right. Transvaginal ultrasound showed a retroverted uterus of normal size and appearance, with an endometrial thickness of 5 mm. The uterine cavum was empty. The left ovary appeared normal in size and echotexture. On the right side, a sausage-shaped adnexal mass measuring 87 x 58 mm was identified. The mass contained a cystic component measuring 58 x 36 mm and a solid component that likely represented a hematoma extending

into the Douglas pouch. Laboratory findings revealed elevated inflammatory markers (leucocytes 18 x 10^9, CRP 198.8 mg/l), and the patient was anemic. Serum human chorionic gonadotropin (hCG) was within normal limits. She was admitted for further evaluation and preoperative preparation. During surgery, extensive adhesions were found between the ascending colon and terminal parts of sigmoid colon and the adnexa bilaterally, as well as with the posterior aspects of the uterus. Following massive adhesiolysis, the mass within the Douglas pouch was accessed and gradually separated from the peritoneum. It resembled a hematoma. The left ovary and fallopian tube were found to be normal in both size and structure. On the right side, the ovary and fallopian tube were found in torsion – three full rotations around the ovarian tube and the utero-ovarian ligament. The fallopian tube was distended, filled with blood clots, and showed a visible rupture site. A right adnexectomy was performed. Hemostasis was secured, and peritoneal lavage was carried out. No intestinal injury was noted, aside from tissue induration. Other abdominal organs appear normal. A drain was placed in the Douglas pouch, and the resected tissue was sent for histopathological analysis. Postoperatively, the patient received analgesics, antibiotics, thromboprophylaxis, and gastroprotective agents. Inflammatory markers and hemoglobin levels were monitored. The patient was discharged after clinical stabilization and normalization of laboratory findings. Histopathological analysis revealed a blood clot with ovarian serosa and hilum tissue.

Case 3

The third patient was admitted to the Gynecology Department due to abdominal pain and dysuria persisting for seven days, accompanied by a fever of 38.5 °C. She was hemodynamically stable, without nausea or vomiting. Transvaginal ultrasound revealed a cystic lesion on the left ovary, measuring 66.2 x 41.8 mm, with opalescent contents, thin smooth walls, and peripheral (marginal) vascularity. Color Doppler imaging showed no blood flow within the cyst and slightly elevated resistance indices. The uterus and left ovary appeared normal. Laboratory investigations showed an elevated CRP level of 37.9 mg/l. Hematological and biochemical parameters were within normal limits. Tumor marker levels were also within the reference range: CA-125 at 17.8 U/ml and CA 19-9 at 4.2 U/ml. Initial conservative treatment yielded no clinical improvement, prompting the decision to proceed with surgical management. Laparotomy was performed via a Pfannenstiel incision. Intraoperative findings included a normal-sized, anteverted and anteflexed uterus with smooth, pink serosa. The right ovary appeared normal in size and structure. The left ovary was cystic and had undergone 180–degree torsion, with extensive adhesions to the small intestine and sigmoid colon. Following careful adhesiolysis, a left adnexectomy was performed. Staging procedure was completed, and the surgical specimen was sent for histopathological analysis. Histology confirmed the diagnosis of torsion of a follicular cyst and a serous paraovarian cyst.

Case 4

A 47-year-old woman was referred to the Gynecology Department for elective surgical treatment of a left ovarian tumefaction. She reported occasional dull pelvic pain. Preoperative investigations revealed normal levels of tumor markers, including cancer antigen (CA) 125, CA 19-9, human epididymis protein 4 and normal ROMA index. Her complete blood count and inflammatory markers were also within normal limits. We found a firm, smooth and immobile tumefaction on the right. Ultrasound examination revealed a heteroechogenic tumefaction measuring 10 cm in diameter, along with a small volume of fluid in the Douglas pouch. Intraoperatively, the left ovary was found to be enlarged – approximately the size of a clenched fist – partially firm and partially cystic, and twisted twice around the mesovarium. It was displaced anteriorly and to the right of the uterus. The surface of the tumefaction appeared necrotic, smooth, and shiny, with no surface excrescences. The left fallopian tube appeared normal. The right ovary and fallopian tube were also of normal appearance. The uterus behind the tumefaction appeared normal but contained several intramural myomas. The other abdominal organs appeared normal. No secondary deposits of the peritoneum were found. Lavage fluid was obtained for cytological examination. Following detorsion and tumefaction extraction, the ligaments were clamped, and a classic left adnexectomy and hysterectomy were performed. Biopsies of the omentum and peritoneum were taken, and the abdomen was closed. Histopathological analysis confirmed torsion of an ovarian fibrothecoma with cystic degeneration and hemorrhage. All other findings were normal. The patient had an uneventful postoperative recovery and was discharged five days after surgery.

Discussion

This case series highlights several distinct causes and clinical presentations of ovarian torsion, along with corresponding laboratory findings, diagnostic approaches and treatment modalities. Known risk

factors for ovarian torsion include adnexal masses, enlarged ovaries, elongated ovarian ligaments in premenarchal girls, and the presence of pelvic adhesions [10]. The diagnosis of ovarian torsion requires a combination of anamnestic data, objective examination, and imaging studies [1]. Patients may report a recent diagnosis of an adnexal mass, recurrent abdominal pain, vomiting, fever, or a history of abdominal surgery [11]. Most abdominal surgeries result in the formation of adhesions, which eventually cause organ fixation. The overall incidence of adhesions is 90% after laparotomy and 55-100% following common pelvic surgeries [12,13]. As a late complication, adhesions may lead to organ strangulation, chronic abdominal pain, female subfertility, or complications during reoperations [12]. In the first case, strangulation of the mesovarium was caused by adhesions following a previous appendectomy and salpingectomy, resulting in hemorrhagic infarction of the ovary. The most common symptom of ovarian torsion is sudden-onset, sharp lower abdominal or pelvic pain, often accompanied by nausea and vomiting in approximately 70% cases [1,14,15]. The pain is typically intermittent, poorly responsive to analgesics, and may radiate to the inguinal region or into the leg [1,8]. On physical examination, clinical suspicion should be raised in the presence of abdominal pain and tenderness and, occasionally, a pelvic mass [8,16]. Laboratory investigations should include at least hematocrit, leukocyte count, HCG, electrolyte levels, and inflammatory markers – CRP. While laboratory findings may be normal, they can also indicate anemia in cases of ovarian rupture or leukocytosis, or elevated CRP in the presence of necrosis and consequential inflammation [17]. The second case illustrates a scenario where ovarian and tube torsion led to pelvic hemorrhage, formation of an organized hematoma, intestinal adhesions, and localized peritonitis, which may progress to sepsis. The patient reported severe pain lasting several days, potentially explaining the complete necrosis of the ovary and the absence of ovary tissue on histopathological examination.

Imaging, particularly ultrasonography, plays a crucial role in the diagnosis. In adult women, transvaginal ultrasound is the first-line imaging modality, with high specificity but variable sensitivity (35-85%). Ultrasound allows assessment of ovarian volume, edema, adnexal masses, free abdominal fluid, and vascular flow using Doppler imaging [18,19]. A significant discrepancy in ovarian volume, coupled with ovarian displacement, is pathognomonic for torsion. Other typical findings include peripheral ovarian follicles with hyperechogenic halos ("string of pearls" sign), and rounded, edematous ovaries. Doppler may show normal, reduced, or absent flow, and small amounts of free fluid may be observed in the pouch of Douglas [1,19].

Functional ovarian cysts are benign lesions that can be managed expectantly, treated medically with progestins, or surgically [20,21]. One of the risks of conservative management is torsion, especially when adnexal masses exceed 5 cm in diameter [22]. In the third case, a large follicular cyst in sub-torsion had formed adhesions to adjacent bowel loops, likely due to local exudation. The patient had prolonged pain and elevated inflammatory markers. Doppler ultrasound showed marginal blood flow with mildly elevated resistance indices.

The fourth case illustrates torsion of a benign ovarian tumor – a fibrothecoma – detected incidentally during elective surgery. Fibrothecomas are the most common ovarian stromal tumors and may occur at any age, though they are most frequently seen between the fourth and sixth decades of life. These tumors are usually asymptomatic but can become symptomatic when torsion occurs [23]. Surgery served both diagnostic and therapeutic purposes in ovarian torsion. A key component of surgical management is minimization the duration of ischemia, although the precise threshold for irreversible ovarian damage remains unknown [1,22]. Intraoperative assessment of ovarian tissue viability is essential [8]. Complete necrosis may present as a gelatinous, disintegrating mass upon manipulation. The best–case surgical scenario includes detorsion alone or detorsion followed by ovariopexy. Ovarian cystectomy is preferred when benign pathology is confirmed [24], while salpingo-oophorectomy in indicated in cases of suspected malignancy, confirmed necrosis, or in postmenopausal women.

Conclusion

Ovarian torsion most commonly affects women of reproductive age and is frequently associated with adnexal masses. Although uncommon and usually of benign etiology, ovarian torsion can cause acute abdominal symptoms and may necessitate emergency surgical intervention. On the other hand, the diagnosis of ovarian torsion is often missed, and ovarian salvage is rare. Timely diagnosis is essential to preserve ovarian function, prevent complications, and optimize reproductive outcomes.

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SURVIVAL AGAINST THE ODDS – ECMO IN POSTCARDIOTOMY CARDIOGENIC SHOCK

PREŽIVLJAVANJE UPRKOS SVEMU – EKMO U POSTKARDIOTOMIJSKOM KARDIOGENOM ŠOKU

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Case report
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Abstract

Introduction. Postcardiotomy cardiogenic shock is a severe complication of cardiac surgery, often requiring mechanical circulatory support and associated with high mortality. We present a case illustrating the complex management of biventricular failure, atrial fibrillation, and ischemic cardiomyopathy from emergency admission to surgical recovery. **Case Report**. A 67-year-old man presented with dyspnoea, hypotension, and facial and peripheral oedema. Echocardiography revealed severe biventricular dysfunction with a left ventricular ejection fraction of 15%, right ventricular failure, and severe tricuspid regurgitation. On admission, he developed atrial fibrillation, managed with inotropes, diuretics, and cautious rate control. Diagnostic work-up revealed multivessel coronary and significant carotid artery disease. The patient underwent urgent triple coronary artery bypass grafting, tricuspid annuloplasty, left carotid endarterectomy, box pulmonary vein isolation, and left atrial appendage occlusion. Intraoperatively, refractory cardiogenic shock necessitated veno-arterial extracorporeal membrane oxygenation with left ventricular venting. Mechanical circulatory support was successfully weaned after three days as cardiac function improved. Postoperative recovery was complicated by *Clostridioides difficile* enterocolitis and fungal pneumonia. He was discharged on postoperative day 36, and at six months remained clinically stable with improved functional capacity. **Conclusion**. This case underscores the importance of a multidisciplinary approach in managing complex cardiac patients. Early hemodynamic assessment, individualized therapy, and timely initiation of extracorporeal membrane oxygenation were critical to survival. In this setting, extracorporeal membrane oxygenation proved to be an effective bridge to recovery, emphasizing its value in select high-risk cases of postcardiotomy cardiogenic shock.

Key words: Shock, Cardiogenic; Thoracic Surgery; Cardiac Surgical Procedures; Extracorporeal Membrane Oxygenation; Extracorporeal Circulation; Risk Factors; Treatment Outcome

Sažetak

Uvod. Postkardiotomijski kardiogeni šok je ozbiljna komplikacija nakon kardiohirurških intervencija, koja često zahteva mehaničku cirkulatornu podršku i povezana je sa visokom smrtnošću. Ovaj prikaz slučaja ilustruje složeno lečenje biventrikularne slabosti, atrijalne fibrilacije i ishemijske kardiomiopatije od hitnog prijema do oporavka nakon operacije. **Prikaz slučaja.** Muškarac star 67 godina primljen je u urgentni centar sa dispnejom, hipotenzijom, otokom lica i ekstremiteta. Ehokardiografijom je utvrđena teška biventrikularna disfunkcija, sa ejekcionom frakcijom leve komore od 15%, insuficijencijom desne komore i teškom trikuspidalnom regurgitacijom. Pri prijemu je razvijena atrijalna fibrilacija, koja je lečena inotropima, diureticima i pažljivom kontrolom frekvencije. Dijagnostika je pokazala višesudovnu koronarnu bolest i značajnu stenozu karotida. Pacijent je hitno operisan: urađena je trostruka aortokoronarna bajpas operacija, anuloplastika trikuspidalne valvule, endarterektomija leve karotidne arterije, izolacija plućnih vena i okluzija apendiksa leve pretkomore. Tokom operacije razvio se refraktarni kardiogeni šok koji je zahtevao veno-arterijsku ekstrakorporalnu membransku oksigenaciju sa ventingom leve komore. Mehanička cirkulatorna podrška je uklonjena nakon tri dana, kada je došlo do poboljšanja srčane funkcije. Postoperativni tok bio je komplikovan enterokolitisom izazvanim *Clostridioides difficile* i gljivičnom pneumonijom. Pacijent je otpušten iz bolnice 36. postoperativnog dana i šest meseci kasnije je bio stabilan, sa poboljšanom funkcionalnom sposobnošću. **Zaključak.** Ovaj prikaz slučaja ističe značaj multidisciplinarnog pristupa u lečenju kompleksnih kardioloških pacijenata. Rano hemodinamičko procenjivanje, individualizovana terapija i pravovremena primena ekstrakorporalne membranske oksigenacije bile su ključne za preživljavanje. Ekstrakorporalna membranska oksigenacija se pokazala kao efikasan most ka oporavku u slučajevima postkardiotomijskog kardiogenog šoka, što naglašava njegov značaj u selektovanim visokorizičnim slučajevima.

Ključne reči: kardiogeni šok; grudna hirurgija; kardiološke hirurške procedure; ekstrakorporalna oksigenacija; ekstrakorporalna cirkulacija; faktori rizika; ishod lečenja

Introduction

Cardiogenic shock is defined by the International Society for Heart and Lung Transplantation/Heart

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Abbreviations

SCAI	– Society for Cardiovascular Angiography and Interventions
POCUS	– point of care ultrasonography
LV	– left ventricular
LVEF	– left ventricular ejection fraction
VTI	– velocity time interval
ECMO	– extracorporeal membrane oxygenation
RSPV	– right superior pulmonary vein
MCS	– mechanical circulatory support

Failure Society of America guideline on acute mechanical circulatory support as a state of tissue hypoperfusion and end-organ dysfunction caused by a primary cardiac disorder with reduced cardiac output. It may present in different stages, as categorized by the Society for Cardiovascular Angiography and Interventions (SCAI) [1,2]. Despite advances in therapy, cardiogenic shock remains a highly fatal and morbid syndrome arising from various cardiovascular conditions. With the growing burden of cardiovascular disease in an aging population, the prevalence of both low cardiac output syndrome and its most severe manifestation – cardiogenic shock – is expected to rise [3]. Physicians across emergency medicine, cardiology, intensive care, and cardiac surgery are therefore increasingly confronted with such patients.

The management aims to restore perfusion and stabilize oxygen delivery to prevent multi-organ dysfunction. This typically involves a stepwise and coordinated approach with volume optimization, diuretics, inotropes, vasopressors and vasodilators [3]. The benefit of levosimendan in this setting remains controversial [4–6]. When medical and surgical interventions fail to achieve hemodynamic stability, mechanical circulatory support (MCS) becomes necessary [7].

We report the case of an adult male with cardiogenic shock, initially managed in the emergency department, subsequently treated in a cardiac surgery unit, and ultimately discharged home following recovery.

Case Report

Patient History and Presentation

A 67-year-old male with a history of hyperlipidaemia and right-sided femoropopliteal bypass presented with bilateral leg oedema, ascites, tachypnoea, and dyspnoea. The dyspnoea occurred both in the supine position and on exertion, accompanied by a sensation of choking, but improved when seated. He also reported several months of progressive decline, a dry cough, and recent dizziness.

On admission, he was relatively hypotensive (100/68 mmHg), tachycardic, and tachy-dyspnoeic. Clinical examination revealed bilateral heart failure, including facial and tongue oedema, dilated jugular veins, and bilateral inspiratory crackles and expiratory wheezing. Breath sounds were absent over the right lower lung field. His abdomen was distended but non-tender, and both lower extremities were swollen below the knees. The patient was obese with a body mass index of 36.6.

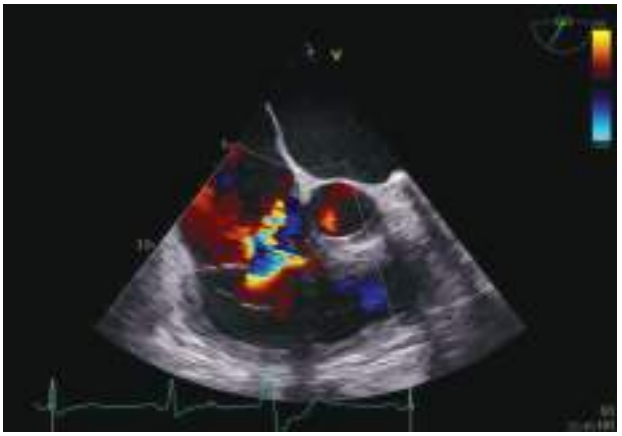

Figure 1. Ultrasound showing severe tricuspid regurgitation

Diagnosis and Intervention

Electrocardiography showed sinus tachycardia at 114 bpm with Q waves in precordial leads V1-3 and low-amplitude T waves in aVL.

Point-of-care ultrasonography (POCUS) in the emergency department revealed a reduced left ventricular ejection fraction of 15%, degenerative changes in the aortic valve, and diminished function of the right ventricle with severe tricuspid regurgitation, later confirmed on transoesophageal echocardiography **(Figure 1).** Fluid status showed dilated inferior vena cava with minimal respiratory modulation, and right-sided pleural effusion **(Figure 2)** with B-profile in multiple lung zones including both-sided anterior

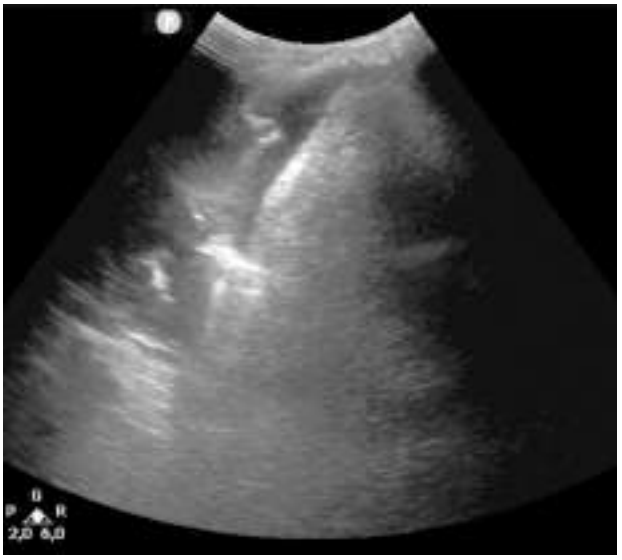

Figure 2. Echo of right pleural effusion on admission

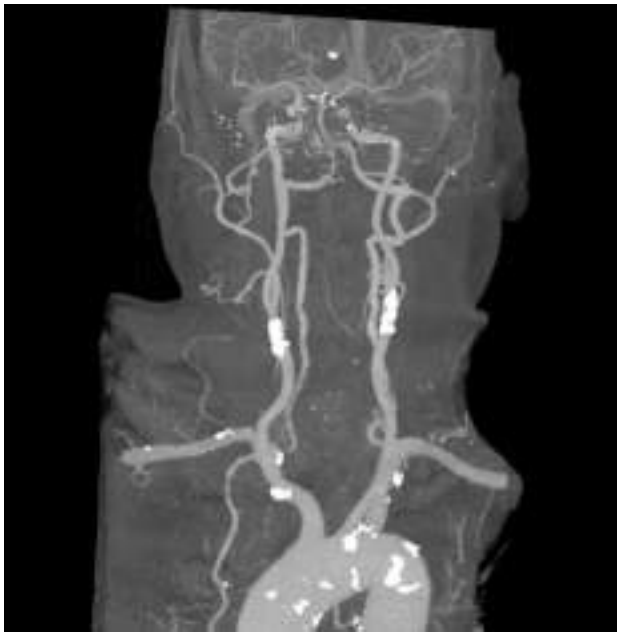

Figure 4. Computed tomography scan revealing significant bilateral carotid stenoses

axillary line and free fluid in the abdomen. The X-ray confirmed a right pleural effusion. Laboratory analyses revealed an elevated serum N-terminal pro b-type natriuretic peptide level of 3863 ng/L.

The patient was started on continuous intravenous furosemide followed by dobutamine. Transient non-invasive positive pressure ventilation was used for respiratory support. During treatment, he developed atrial fibrillation with a rapid ventricular response of 188 bpm, for which amiodarone and therapeutic-dose low molecular weight heparin were initiated.

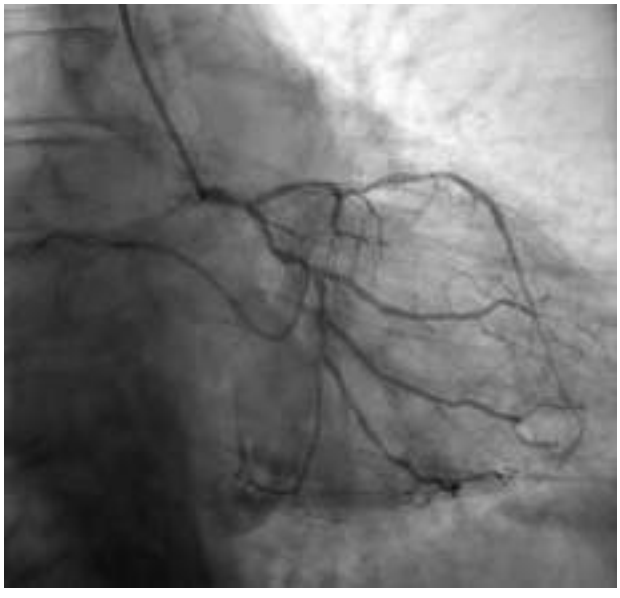

Figure 3. Coronary artery angiogram showing significant left main stenosis, subtotal LAD, and several circumflex stenoses

Coronary angiography demonstrated severe obstructive three-vessel coronary disease, with >50% left main stenosis and an occluded right coronary artery **(Figure 3).** Myocardial perfusion scintigraphy showed non-viable apex and lower half of the septum. Computed tomography angiography identified a subtotal stenosis of the left internal carotid with an 80% stenosis of the right internal carotid artery **(Figure 4).**

After stabilization and diagnostics, the patient underwent triple coronary artery bypass grafting, left carotid endarterectomy, tricuspid annuloplasty, radiofrequency ablation, and left atrial appendage occlusion. Weaning from cardiopulmonary bypass was complicated by refractory cardiogenic shock (LVEF 5%, (velocity time interval (VTI) 8 cm), requiring initiation of extracorporeal membrane oxygenation (ECMO) with left ventricular (LV) venting via the right superior pulmonary vein (RSPV). He required high-dose continuous inotropic support (epinephrine, milrinone, dobutamine) and vasopressors (norepinephrine, vasopressin). After 70 hours, ECMO was safely removed following improved LV function (LVEF 25%, VTI 12 cm). Postoperatively, recovery was prolonged due to *Clostridioides difficile* enterocolitis and *Candida parapsilosis* pneumonia **(Figure 5).**

Outcome

The patient was discharged on postoperative day 36. At six-month follow-up, he remained clinically stable with improved functional capacity and was managed on an outpatient basis.

Conclusion

This case report underscores the multifaceted challenges encountered in the emergency and surgi-

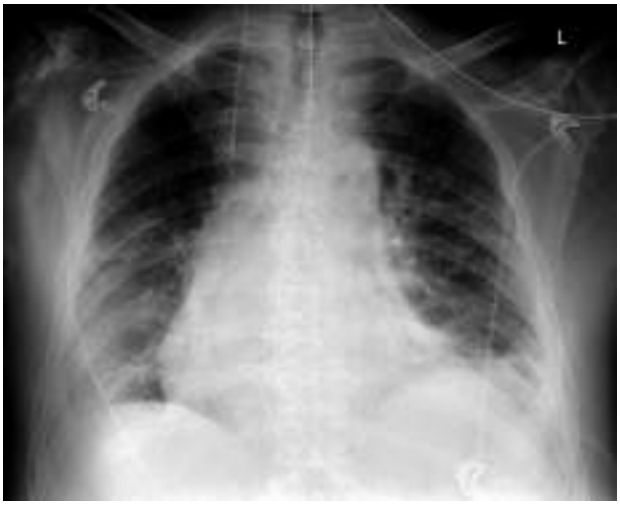

Figure 5. Postoperative chest X-ray confirming diffuse bilateral pulmonary infiltrates

cal management of postcardiotomy cardiogenic shock, highlighting extracorporeal membrane oxygenation as a life-saving intervention [2,7,8]. The patient presented with severe biventricular failure and multi-organ dysfunction (Society for Cardiovascular Angiography and Interventions stage B (1)), necessitating a complex sequenced combination of medical, interventional, and surgical therapies.

From an emergency medicine perspective, this case emphasized the pivotal role of early echocardiographic assessment in guiding acute management, including the initiation of non-invasive positive pressure ventilation and continuous infusion diuretics [9]. The occurrence of tachycardic atrial fibrillation in a patient with ischemic cardiomyopathy illustrated a critical therapeutic dilemma – balancing rate control, hemodynamic support, and anticoagulation without exacerbating hypotension or further impairing cardiac output [10].

The surgical phase highlights the extreme risk posed by concomitant multivessel coronary artery disease and valvular pathology in the context of profound hemodynamic instability. The patient's estimated morbidity & mortality risk according to the Society of Thoracic Surgeons score was 70%, with a 60% likelihood of prolonged ventilation estimation and a 45% probability of hospital stay exceeding 14 days. The necessity of performing coronary artery bypass grafting, tricuspid valve repair, ablation, and left atrial appendage occlusion in a single procedure reflects the complexity of perioperative management at Society for Cardiovascular Angiography and Interventions stage D (1). The use of extracorporeal membrane oxygenation for refractory postcardiotomy shock demonstrates its evolving role in cardiac surgery and critical care, serving as an effective bridge to recovery while mitigating low cardiac output syndrome. Importantly, our institution has recently updated our left ventricular unloading technique from concomitant intra-aortic balloon pump [11] to right superior pulmonary vein vent placement.

Postoperative complications – including *Clostridioides difficile* enterocolitis, fungal pneumonia, and the need for prolonged rehabilitation – further illustrate the vulnerability of this patient population [12]. Nevertheless, the patient's successful discharge and six-month clinical stability underscore the value of multidisciplinary collaboration, timely mechanical circulatory support initiation, and structured long-term follow-up [13].

A recently proposed dynamic scoring tool, the Houston Severity, Hemodynamics, Onset, Causes, and Kinetics Score, integrates temporal changes in cardiogenic shock severity [14]. In our patient, the score was 2 at emergency department presentation – prompting escalation of management – and later increased to 3 perioperatively, indicating the need for urgent mechanical circulatory support. We found the Houston Severity, Hemodynamics, Onset, Causes, and Kinetics Score to be a practical, intuitive, and clinically useful framework for guiding decision-making in critically ill patients [14].

This case serves as an exemplary reference for managing high-risk cardiac surgical patients, and underscores the need for further research into optimal perioperative hemodynamic support strategies to improve survival outcomes in this complex population.

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IN MEMORIAM
IN MEMORIAM

Akademik ZORAN L. KOVAČEVIĆ (1935–2025)

Akademik Zoran L. Kovačević, lekar, profesor biohemije u penziji, redovni član SANU, preminuo je 22. juna 2025. u Sremskoj Kamenici, u devedesetoj godini.

Rođen je 23. septembra 1935. u Popincima u Sremu, gde je završio osnovnu školu, a gimnaziju 1955. u Zemunu. Diplomirao je na Medicinskom fakultetu u Beogradu 1962. godine. Kao stipendista Medicinskog fakulteta u Novom Sadu (MFNS) izabran je 1963. godine za asistenta na biohemiji i za saradnika Instituta za medicinska istraživanja.

Kao stipendista Fonda za naučni rad Srbije, boravio je 1969. u Bristolu u Engleskoj na stručnom usavršavanju, a 1970. radio je u Nacionalnom medicinskom centru u Los Anđelesu. Čuveni profesor Harold P. Moris, omogućio mu je rad na seriji transplantabilnih tumora jetre. Na MFNS je 1971. odbranio doktorsku disertaciju „Oksidativni metabolizam glutamina normalnih i malignih ćelija". Organizovao je 1971. laboratoriju za proučavanje celularne energetike, prve te vrste u našoj zemlji. Uveo je metode frakcionisanja ćelija i proučavanja metabolizma i enzima na celularnom i supcelularnom nivou.

Ključni naučni doprinosi akademika Kovačevića, publikovani u preko 100 naučnih radova, odnose se na dokaz mehanizma transfera redukcionih ekvivalenata iz citoplazme u mitohondrije, određivanje supcelularne lokalizacije enzima glutaminaze i mehanizma transporta glutamina u mitohondrije, kao i dokaz da maligne ćelije koriste glutamin kao energetski supstrat.

Usavršavao se u Nemačkoj, u SAD i Kanadi. Bio je predavač po pozivu na brojnim naučnim skupovima i gost-predavač na mnogim svetskim univerzitetima.

Za redovnog profesora na Katedri za biohemiju izabran je 1985. godine, a od 1982. bio je načelnik Instituta za biohemiju i šef Katedre za biohemiju do penzionisanja 2002. godine.

Za dopisnog člana Vojvođanske akademije nauka i umetnosti izabran je 22. novembra 1984., a za redovnog člana 3. decembra 1990. Nalazio se na dužnosti sekretara Odeljenja za prirodne nauke VANU (1988–1990). Akademsku besedu u VANU održao je 15. decembra 1992. pod naslovom „Evolucioni i funkcionalni aspekt maligne alteracije ćelije". Integracijom akademija 29. maja 1991. postao je redovni član Odeljenja medicinskih nauka SANU. Bio je predsednik Ogranka SANU u Novom Sadu i član Izvršnog odbora i Predsedništva SANU (2002–2015).

Izabran je 1994. za redovnog člana Medicinske akademije Srpskog lekarskog društva. Bio je predsednik Biohemijskog društva Vojvodine, član Predsedništva Saveza biohemijskih društava Jugoslavije, član Biohemijskog društva Velike Britanije, Evropske akademije nauka i umetnosti iz Salcburga, inostrani član Crnogorske akademije nauka i umjetnosti.

Dobitnik je najznačajnijih priznanja, kao što su Nagrada za naučni rad SLD (1993), Zlatna plaketa sa medaljom Univerziteta u Novom Sadu za životno delo, Nagrada za najcitiranijeg naučnika Vojvodine koju dodeljuje Pokrajinski sekretarijat za nauku Vojvodine (2010). Odlikovan je Sretenjskim ordenom prvog stepena (2024).

Sa suprugom Borislavom rođ. Mužijević, profesorom srpskog jezika i književnosti, akademik Kovačević ima sina Branislava Kovačevića, doktora poljoprivrednih nauka, i dr Maju Stefanović, doktora medicinskih nauka i docenta na MFNS, i šestoro unučadi.

Akademik Kovačević ostaje u trajnom sećanju brojih generacija studenata, specijalista i doktora nauka na MFNS, koje je inspirisao svojim izvanrednim predavanjima koja se pamte, kao i svojim udžbenicima, monografijama i knjigama, koji se na aktuelan, savremen i interesantan način bave važnim temama u medicinskoj nauci i predstavljaju trajno zaveštanje budućim generacijama.

Slava mu i hvala!

Prof. dr Karmen Stankov

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