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# EDITORIAL
# *UVODNIK*

## DEVELOPING MENTAL HEALTH CARE IN THE COMMUNITY

## *RAZVOJ ZAŠTITE MENTALNOG ZDRAVLJA U ZAJEDNICI*

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Editorial
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Mental health is a state of well-being in which individuals realize their own abilities, manage the normal stresses of life, work productively, and contribute to their communities [1]. It is an integral component of the overall health and well-being for individuals, families, and broader communities.

Mental health, both at the individual and social level, depends on various factors, including genetic predisposition, psychological traits, and, to a significant extent, the environment in which a person is raised and lives. Key influences also include family dynamics, economic and social conditions, and community support. Among these, social determinants of health play a leading role in safeguarding mental well-being. Addressing the social determinants of health to improve mental health necessitates a multisectoral, multidisciplinary approach involving the entire community.

Despite increasing awareness of mental health's importance, stigma, resource scarcity, and inadequate healthcare system responses continue to hinder progress in this area. This is especially evident within communities, which serve as the primary framework for supporting and rehabilitating individuals with mental disorders.

Communities play a pivotal role in fostering mental health, preventing disorders, and supporting those facing mental health challenges. Community-based models, such as mobile mental health teams, support groups, and local integration programs, have demonstrated success in reducing hospitalizations and enhancing users' quality of life. Within the community, individuals can access opportunities for social reintegration, employment, and the support networks essential for recovery.

The contributions of family, friends, workplaces, and local organizations underscore the importance of education and empowerment in providing mental health support. Community mental health services prioritize patient autonomy and independence. In the therapeutic process aimed at recovery, social support plays a crucial role. Within the biopsychosocial approach to treating mental disorders, social therapy focuses on enhancing resilience and reinforcing a person's remaining capacities for reintegration into the community. A community's willingness to accept and include a person in daily activities through various support services is the guarantor of faster and more effective recovery, as well as the overall quality of mental health care [2, 3]. Those for whom mental care is intended – users and their families – should play an essential role in shaping health policies and interventions. Empowering users through peer support initiatives and engaging experts by experience as peer workers within health and social care systems reduces stigma, fosters empathy and understanding, and eases demand on healthcare resources.

Interventions delivered through various health and social services aim to empower individuals to take full responsibility for their health. These interventions are grounded in a personalized approach, emphasizing individual recovery plans. Recovery, as a therapeutic goal, entails reintegration into the community [4].

However, several obstacles hinder the development of these approaches, including limited financial resources, insufficient integration of mental health services into primary care, and pervasive stigma in many communities. A lack of trained professionals, particularly in rural and underdeveloped areas, further complicates the provision of comprehensive support.

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The COVID-19 pandemic has exposed the fragility of mental health systems, with heightened loneliness, anxiety, and depression underscoring the urgent need to strengthen community resources and improve coordination between healthcare systems and broader social networks [5].

To address these challenges, sustainable models for community mental health support must be developed, including:

1. Strengthening primary healthcare: by integrating mental health services to improve accessibility and affordability.

2. Education and destigmatization by implementing campaigns and programs to foster understanding and empathy toward individuals with mental health disorders.

3. Increased investment by allocating resources for skilled personnel, infrastructure, and digital tools, particularly in remote areas.

4. Support for families and informal caregivers by providing specialized programs and counseling services.

5. Intersectoral collaboration by encouraging cooperation among healthcare, education, social services, and non-governmental organizations to create joint solutions.

Community mental health extends beyond healthcare; it is a societal priority. Investing in robust community mental health resources ensures a healthier, more resilient and compassionate society. Mental health must occupy a central position in health and social policy planning. Our communities have the potential not only to provide support but also to become key players in creating a more inclusive and humane society [6].

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ORIGINAL STUDIES
*ORIGINALNI NAUČNI RADOVI*

# CORRELATION BETWEEN AGE, STATE OF CONSCIOUSNESS, AND FINDINGS ON COMPUTED TOMOGRAPHY OF THE BRAIN IN PATIENTS WITH MILD TRAUMATIC BRAIN INJURY

## *POVEZANOST STAROSNE DOBI, STANJA SVESTI I NALAZA NA KOMPJUTERIZOVANOJ TOMOGRAFIJI MOZGA KOD PACIJENATA SA BLAGIM TRAUMATSKIM MOŽDANIM OŠTEĆENJEM*

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**Abstract**

**Introduction.** Traumatic brain injury affects over 50 million people worldwide annually, with mild traumatic brain injury accounting for approximately 80%. The number of elderly patients sustaining such injuries is increasing. This study aimed to compare differences in consciousness impairment and computed tomography findings among mild traumatic brain injury patients of different age groups upon hospital admission. **Material and Methods.** This retrospective study included 150 patients with mild traumatic brain injury hospitalized at the Neurosurgery Clinic of the Clinical Center of Vojvodina between January 1, 2020 and July 1, 2021. Patients were categorized into three age groups and compared based on the level of consciousness impairment, assessed using the Glasgow Coma Scale, and computed tomography findings evaluated using the Rotterdam score. **Results.** Statistical analysis revealed that the mean Rotterdam score was 1.6 in patients aged 18-30 years, 1.64 in those aged 31-65 years, and 2.36 in patients over 65 years. The difference between the mean Rotterdam scores between the oldest group and other two groups was highly statistically significant. **Conclusion.** The findings indicate a significant correlation between age and injury severity, with older patients exhibiting more severe computed tomography findings. However, impairment of consciousness at admission remained comparable across all age groups.

**Key words:** Brain Concussion; Consciousness; Tomography, X-Ray Computed; Age Factors; Glasgow Coma Scale

**Sažetak**

**Uvod.** U svetu više od 50 miliona ljudi godišnje pretrpi traumatsko moždano oštećenje što predstavlja rastući zdravstveno-socijalni problem. Najveći broj povređenih je u grupi sa blagim traumatskim moždanim oštećenjem, oko 80%. Takođe je rastući broj povređenih starije životne dobi. Ciljevi ovog istraživanja bili su: Poređenje razlika povređenih sa blagim traumatskim moždanim oštećenjem različitih životnih dobi u odnosu na poremećaj stanja svesti nalazom kompjuterizovane tomografije prilikom prijema u bolnicu. **Materijal i metode.** Retrospektivna studija obuhvatila je 150 povređenih sa blagim traumatskim moždanim oštećenjem koji su hospitalizovani na Klinici za neurohirurgiju Univerzitetskog kliničkog centra Vojvodine u periodu od 1. 1. 2020. do 1. 7. 2021. godine. Povređeni su prema starosti podeljeni u tri grupe. Grupe se poređene u odnosu na poremećaj stanja svesti povređenih (vrednovan *Glazgovskom koma skalom*) i nalaz pregleda kompjuterizovane tomografije (vrednovan *Roterdamskim skorom*). **Rezultati.** Statističkom obradom dobijeno je da je prosečna vrednost *Roterdamskog skora* u grupi povređenih od 18 do 30 godina iznosila 1,6; prosečna vrednost skora u grupi povređenih od 31 do 65 godina iznosila je 1,64, dok je u grupi povređenih starijih od 65 godina iznosila 2,36. Razlika između prosečnih vrednosti skorova između starijih od 65 i ostale dve grupe je visoko statistički značajna. **Zaključak.** Rezultati ove studije ukazuju na statistički značajnu razliku prosečne vrednosti *Roterdamskog skora* kod povređenih sa blagim traumatskim moždanim oštećenjem različitih životnih grupa u smislu da stariji povređeni imaju teže povrede, dok je poremećaj stanja svesti svih ispitanih grupa na prijemu bio isti.

**Ključne reči:** traumatsko moždano oštećenje; stanje svesti; kompjuterizovana tomografija; uzrast; Glazgov koma skor

## Introduction

Traumatic brain injury (TBI) refers to structural brain damage and/or alternations in the physiological brain function resulting from an external mechanical force. It is classified as mild, moderate, or severe [1]. Each year, more than 50 million people worldwide experience TBI, making it a growing public health

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***Abbreviations***

| | |
|---|---|
| TBI | – traumatic brain injury |
| MTBI | – mild traumatic brain injury |
| GCS | – Glasgow Coma Scale |
| CT | – computed tomography |
| OAC | – oral anticoagulant |
| AP | – antiplatelet |
| APT | – antiplatelet therapy |

and societal concern. In Europe, the estimated annual hospitalization rate due to TBI is 262 per 100,000 individuals. The majority of cases - approximately 80% – fall into the category of mild TBI (MTBI) [2, 3]. TBI remains the leading cause of mortality and morbidity in individuals under 45 and is becoming increasingly prevalent among those over 65. Moreover, it is a major contributor to long-term disability, affecting not only survivors but also their families and society as a whole. The financial burden of TBI is substantial, encompassing both direct healthcare and rehabilitation costs as well as indirect costs related to loss of work ability [1, 4]. Additionally, approximately 10% of MTBI cases may lead to adjustment disorders [5].

The Glasgow Coma Scale (GCS) is a widely used tool for assessing consciousness levels and evaluating the severity of neurological impairment following head trauma [6–8]. It consists of three components: eye opening, best verbal response, and best motor response, with total scores ranging from 3 to 15. Patients with a GCS of 15 are fully conscious and responsive, while those with a score of 3 are in deep coma, showing no response to painful stimuli [9]. The severity of TBI is directly correlated with the degree of consciousness impairment and is classified as mild (GCS 13-15), moderate (GCS 9-12), or severe TBI (GCS ≤8) [8].

Computed tomography (CT) has become the gold standard for TBI evaluation due to its ability to detect cranial and intracranial injuries immediately. However, the clinical outcome of TBI remains unpredictable, leading to the development of various prognostic models [10, 11]. Among these, the Rotterdam CT score is widely used tool to predict injury severity. It evaluates initial CT findings based on the condition of the basal cisterns, midline shift, presence of epidural hematoma, and traumatic subarachnoid or intraventricular hemorrhage. The Rotterdam score has demonstrated strong prognostic accuracy and is predominantly applied in moderate and severe TBI cases [12, 13]. Its simplicity, reproducibility, and minimal inter-examiner variability make it a valuable tool for comparing research outcomes across studies and/or institutions [11, 14].

This study aims to:

- Identify differences in MTBI patients of different age groups regarding consciousness impairment and CT findings upon hospital admission.
- Compare gender differences, the impact of oral anticoagulant or antiplatelet therapy, and injury mechanisms in relation to consciousness impairment and CT findings at admission.

We hypothesize that older patients will present with similar levels of consciousness impairment at admission compared to younger patients, but their CT findings will indicate a higher Rotterdam CT score.

Given the potentially severe consequences, the unpredictable outcomes, and the risk of underestimating injury severity in TBI cases, it is essential to further investigate the significance of initial consciousness levels and CT findings at admission across different age groups.

## Material and Methods

This retrospective study included 150 randomly selected patients with MTBI who were hospitalized at the Neurosurgery Clinic of the University Clinical Center of Vojvodina between January 2020 and July 2021. Ethical approval was obtained from the Ethics and Expert Committee of the University Clinical Center of Vojvodina (00-144).

Patients were included if they: had sustained a mild traumatic brain injury, defined by GCS score of 13-15 upon admission, were aged 18 years or older, underwent a cranial CT scan at admission, and had available medical documentation, including reports from a specialist or a resident in emergency medicine or neurosurgery at the time of admission.

Exclusion criteria included: absence of reports from a specialist or a resident in emergency medicine and neurosurgery at admission, lack of cranial CT scan at admission or inadequate imaging for evaluation, GCS scores indicating moderate or severe TBI, and admitted to another clinic within the University Clinical Center of Vojvodina due to more severe primary injury. Based on these criteria, 150 patients were classified into three age groups, with 50 patients in each: Group 1:18-30 years, Group 2:31-65 years, and Group 3:66 years and older.

The following clinical and radiological parameters were analyzed: age, sex, GCS score at admission, mechanisms of injury, use of oral anticoagulant (OAC) or antiplatelet therapy (APT), and CT findings.

Axial cranial CT scans were evaluated by a neuroradiologist and a neurosurgeon using the Vue PACS Carestream program to identify signs of traumatic brain injury. For patients with abnormal CT findings,

the Rotterdam CT score was calculated based on the following criteria:

– Basal cisterns morphology: Normal (0 points), compressed (1 point), or absent (2 points).

– Midline shift, defined as the deviation of the *septum pellucidum* from the line passing along the *falx cerebri*: ≥5 mm (1 point) or <5 mm (0 points).

– Epidural hematoma: Present (1 point) or absent (0 points).

– Traumatic subarachnoid hemorrhage (tSAH) or intraventricular hemorrhage (IVH): Present (1 point) or absent (0 points).

The final Rotterdam CT score was obtained by summing the assigned points and adding 1. The lowest possible score (1) indicated a normal CT scan, while the highest (6) represented the most severe findings. In this study, the Rotterdam CT score was used solely for the numerical assessment of morphological changes on CT scans and not for outcome prediction.

Statistical analysis was conducted using SPSS Statistics 25.0. Data were presented as absolute numbers, percentages, or mean values ± standard deviation in tables or graphs. Normality of distribution was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test and the Kruskal-Wallis test were applied for non-parametric comparisons. A p-value <0.05 was considered statistically significant.

## Results

In the 18-30 age group, 37 participants (74%) were male and 13 (26%) were female **(Figure 1)**, with a mean age of 24.68 ± 3.61 years. The average GCS score was 14.86, with 44 patients (88%) presenting with a GCS of 15, five (10%) with a GCS of 14, and one (2%) with a GCS of 13 **(Figure 2)**. Regarding injury mechanisms, traffic accidents accounted for 48%, followed by assaults (30%), falls from height (10%), and sports injuries, same-level falls, and unspecified mechanisms (4% each) **(Figure 3)**. None of patients in this group were receiving OAC or APT therapy.

In the 31-65 age group, 33 participants (66%) were male and 17 (34%) were female **(Figure 1)**, with a mean age of 47.60 ± 9.56 years. The average GCS score

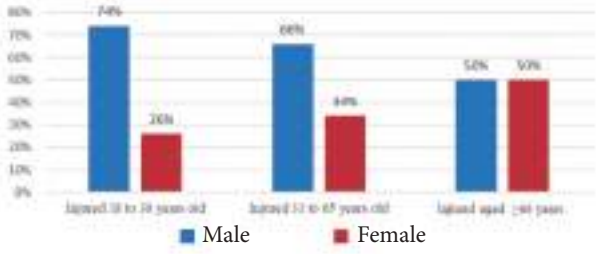


**Figure 1.** Gender distribution in the examined groups

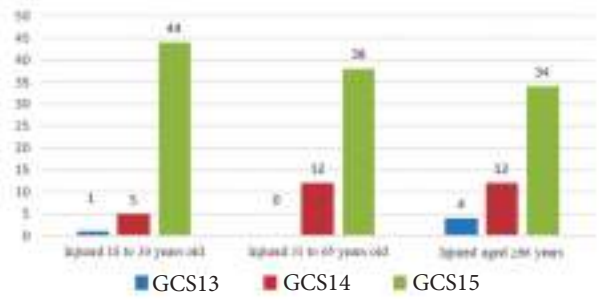


**Figure 2.** Average GCS value among the groups

was 14.76, with 38 patients (76%) scoring 15 and 12 (24%) scoring 14 **(Figure 2)**. Same-level falls and traffic accidents were the most frequent causes (32% each), followed by unspecified mechanisms (16%), falls from height (10%), assaults (8%), and other mechanisms (2%) **(Figure 3)**. Only one patient in this group was on OAC or APT therapy.

In the ≥66 age group, there was an equal distribution of males and females (25 each) **(Figure 1)**, with a mean age of 77.24 ± 7.23 years. The average GCS score was 14.6, with 34 patients (68%) scoring 15, 12 (24%) scoring 14, and four (8%) scoring 13 **(Figure 2)**. Same-level falls were the most common cause (64%), followed by traffic accidents (18%), falls from height (10%), unspecified mechanisms (6%), and assaults (2%) **(Figure 3)**. In this group, 26% of patients were on OAC or APT therapy.

Statistical analysis showed that the mean Rotterdam CT scores were 1.6 in the 18-30 age group, 1.64

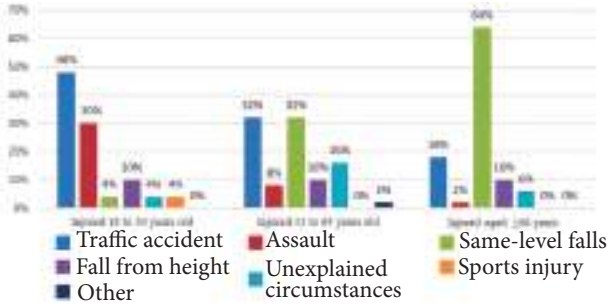


**Figure 3.** Distribution of injury mechanisms in the examined groups


**Figure 4.** Average value of the Rotterdam CT score of all subjects

**Table 1.** Results on the Rotterdam CT score affected by age

| Compared groups | Rotterdam CT score | Mann Whitney U test | p value |
|---|---|---|---|
| Injured aged 18-30 | 1.6 | 615.00 | p<0.001 |
| Injured aged 66 or older | 2.36 | | |
| Injured aged 18-30 | 1.6 | 1230.00 | p=0.734 |
| Injured aged 31-65 | 1.64 | | |
| Injured aged 31-65 | 1.64 | 654.00 | p<0.001 |
| Injured aged 66 or older | 2.36 | | |

in the 31-65 age group, and 2.36 in the ≥66 group **(Figure 4).** A Kruskal-Wallis test showed a statistically significant difference among the three age groups ($\chi^2$=29.29; p<0.001).

The analysis of Rotterdam CT score averages across age groups revealed the following findings: no significant difference was observed between individuals aged 18-30 years and 31-65 years (U = 1230.00, p = 0.734); significant differences were found when comparing individuals aged 18-30 years with those aged 66 or over (U = 615.00, p < 0.001) and between individuals aged 31-65 years and those aged 66 or over (U = 654.00, p < 0.001). In both comparisons involving the ≥66 age group, Rotterdam CT scores were significantly higher **(Table 1).**

Statistically significant differences in mean Rotterdam CT scores were observed across groups based on GCS. No significant difference was found between injured individuals with GCS 13 and GCS 14 (p = 0.393). Significant differences were observed between injured individuals with GCS 13 and GCS 15 (p = 0.05) and between GCS 14 and GCS 15 (p = 0.047). In both cases, Rotterdam CT scores were significantly higher in the lower GCS groups (GCS 13 and 14) compared to GCS 15.

No statistically significant differences in Rotterdam CT score averages were found based on: OAC and/or APT therapy (Mann-Whitney U = 762.00; p = 0.17); Gender (Mann-Whitney U = 2049.00; p = 1.77); Mechanism of injury (Kruskal-Wallis test = 11.32; p = 0.09).

## Discussion

This study revealed difference in gender distribution and injury mechanisms within and between age groups. Among individuals aged 18-30, males accounted for 74% of cases, while females represented 26%. This discrepancy can be attributed to injury mechanism, as 48% of cases were due to traffic trauma, and studies suggest that men are more prone to aggressive and high-risk driving behaviors, increasing the likelihood of accidents [15, 16]. Additionally, 30% of injuries in this group resulted from assaults, where men are also more commonly involved [17, 18]. In the 31-65 age group, 66% of cases involved males and 34% females. The most common injury mechanisms were traffic trauma (32%) and same-level falls (32%). A gradual shift in gender distribution and injury mechanisms were observed with aging. In the ≥66 age group, male and female representation was equal (50% each). This can be explained by the high prevalence (64%) of same-level falls as the leading injury mechanism [19]. The relationship between gender and injury mechanisms observed in this study aligns with previous findings [19–21].

As the global population ages, older individuals are more susceptible to cardiovascular diseases requiring OAC or APT therapy, which increased the risk of severe clinical outcomes following TBI [22]. In this study, 26% of individuals aged ≥66 and one person aged 31-65 were on OAC/APT therapy. Statistical analysis showed no significant difference in Rotterdam CT scores between those using and not using these therapies. However, the average Rotterdam CT score was higher in the older age group, likely due to a greater incidence of hemorrhagic lesions.

Although the Rotterdam CT score is a reliable predictor of TBI outcomes, it has certain limitations. It does not account for lesion size or localization, both of which significantly influence prognosis. It does not include all intracranial abnormalities on CT scans, such as acute subdural hematomas, intracerebral hematomas, brain contusions, or diffuse axonal injury. Subdural hematoma is the most common pathology in elderly patients with same-level falls, which constituted 64% of injury mechanisms in individuals aged ≥66 in this study. If an updated scoring system accounted for subdural hematoma presence, older patients would likely have even higher scores, increasing the difference between age groups [23].

The intracranial space has a fixed volume composed of brain tissue, cerebrospinal fluid, blood vessels, and pathological process. Any increase in volume – as seen in TBI – raises intracranial pressure, leading to symptoms such as altered consciousness, which is assessed using the GCS.

With aging, brain atrophy leads to decrease in brain volume, enhancing the intracranial compensatory capacities. As a result, intracranial hemorrhage can ex-

pand significantly before causing neurological deterioration. This explains why older patients with extensive intracranial pathology may present with relatively mild clinical symptoms at admission, creating a misleading impression of less severe injury. This study included only mild TBI cases (GCS 13-15), meaning all patients had similar clinical presentation at admission. However, according to **Table 1,** older patients (≥66 years) had similar GCS scores to younger patients, despite having more extensive intracranial pathology.

A study at the University of California demonstrated that age affects GCS and Rotterdam CT scores, with older patients exhibiting higher GCS scores at admission despite similar Rotterdam CT scores [24]. Our findings are consistent with this. Additionally, another study found a correlation between older age and better clinical presentation at admission. When injuries were assessed using the Abbreviated Injury Scale (AIS), it was observed that among patients with severe injuries (AIS 5), older individuals typically had mild neurological deficits (GCS 13-15). In contrast, younger individuals had severe neurological deficits (GCS 3-8). However, mortality was higher in the elderly group. In the above study, the patients were divided into two groups: older patients (≥65 years) and younger patients (<65 years). Differences in patient stratification between studies should be considered, as they may influence certain results [8]. A study from Great Britain also found that patients aged ≥65 years had higher GCS scores at admission than patients under 65 years of age for the same injury severity as assessed by AIS [25].

One of the limitations of this study is that the Rotterdam CT score is primarily used for outcome prediction, rather than for evaluating intracranial pathology extent, which was its application here. Additionally, Rotterdam CT scores are mainly used for moderate and severe TBI, whereas this study focused only on mild TBI. As a result, only five patients had a Rotterdam CT score of 4, and no patients had scores of 5 or 6. Future studies should include patients with moderate and severe TBI, allowing for more comprehensive analysis of age-related effects on consciousness impairment and CT findings at admission.

## Conclusion

The study demonstrates a statistically significant difference in Rotterdam computed tomography scores among patients with mild traumatic brain injury aged ≥66 compared to those aged 18-30 and 31-65, indicating that older patients sustain more severe intracranial injuries (higher Rotterdam computed tomography scores).

However, no statistically significant difference was observed in Rotterdam computed tomography scores between the 18-30 and 31-65 age groups.

Additionally, there was no statistically significant difference in Rotterdam computed tomography scores based on gender, mechanism of injury, or the use of oral anticoagulant or antiplatelet therapy. Nevertheless, differences were noted in the distribution of gender, injury mechanisms, and oral anticoagulant/antiplatelet therapy therapy use within and between age groups.

Despite older patients having more extensive intracranial injuries, their level of consciousness at admission Glasgow Coma Scale was comparable to that of younger patients. As a result, older patients may appear less severely injured than they actually are, potentially leading to an underestimation of injury severity.

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# PROXIMAL HUMERUS FRACTURES IN THE PEDIATRIC POPULATION

# *PRELOMI GORNJEG OKRAJKA RAMENICE U PEDIJATRIJSKOJ POPULACIJI*

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**Abstract**

**Introduction.** Pediatric fractures can impose temporary activity restrictions and, in some cases, result in lasting functional limitations. The study examines the distribution of age and gender among affected patients, mechanisms of injury, duration of immobilization, and the prevalence of surgical treatment methods in children with proximal humerus fractures. **Material and Methods.** This retrospective study, conducted between 2016 and 2023, included 249 children (aged 0-17 years), both male and female, with proximal humerus fractures. Statistical analysis was performed using the Mann-Whitney test, Chi-square ($X^2$) test, and post-hoc tests. **Results.** Among the 249 participants, 25 required surgical treatment. The surgical intervention rate increased with age, from 5.1% in children under 7 years to 17.4% in those over 12. Gender did not significantly influence the likelihood of surgical treatment ($p > 0.05$). Traffic accidents were significantly more common in the surgical group (30% vs. 3.7%), suggesting a correlation between high-impact trauma and the need for surgery. Immobilization duration was significantly shorter in non-surgical patients compared to those who underwent surgery ($p < 0.05$). The average hospital stay for surgically treated patients was four days, with treatments including various internal fixation methods. **Conclusion.** Proximal humerus fractures in children occur equally in both sexes, predominantly affecting those aged 7 to 12 years. Falls represent the most common injury mechanism, while traffic-related trauma is more frequently associated with surgical cases. Approximately 10% of children require surgical intervention, particularly older patients due to reduced bone remodeling capacity. Elastic nails and Kirschner wires are effective fixation methods. Further studies should stratify patients based on demographics and fracture classification to optimize treatment strategies and evaluate long-term outcomes.

**Key words:** Humeral Fractures; Shoulder Fractures; Child; Risk Factors; Orthopedic Procedures; Treatment Outcome

**Sažetak**

**Uvod.** Prelomi kod dece mogu dovesti do privremenih ograničenja aktivnosti i do trajnih funkcionalnih ograničenja. Studija je ispitivala starosnu i polnu distribuciju pacijenata, mehanizme povrede, trajanje imobilizacije i prevalenciju hirurških metoda lečenja preloma proksimalnog humerusa kod dece. **Materijal i metode.** Retrospektivna studija, sprovedena od 2016. do 2023. godine, obuhvatila je 249 učesnika uzrasta od 0 do 17 godina, oba pola, koji su zadobili prelome proksimalnog humerusa. Statistička analiza je izvršena korišćenjem Man-Vitnijevog testa, hi-kvadrat ($X^2$) testa i post-hok testova. **Rezultati.** Od 249 učesnika, 25 je lečeno hirurški, sa stopom povećanja sa 5,1% kod onih ispod sedam godina na 17,4% kod pacijenata starijih od 12 godina. Pol nije značajno uticao na stope hirurškog lečenja ($p > 0,05$). Saobraćajni traumatizam je bio češći mehanizam povređivanja u hirurškoj grupi (30% prema 3,7%), što ukazuje na težinu povreda koje su zahtevale operaciju. Nehirurški pacijenti su imali kraće trajanje imobilizacije od hirurških pacijenata, sa značajnom razlikom ($p < 0,05$). Hirurški pacijenti su prosečno boravili u bolnici od četiri dana, uz operacije koje su uključivale različite metode unutrašnje fiksacije. **Zaključak.** Prelomi proksimalnog humerusa kod dece se javljaju podjednako po polu, najčešće kod dece uzrasta od sedam do 12 godina. Padovi su najčešći mehanizam povrede, dok je saobraćajna trauma češća u hirurškim slučajevima. Oko 10% pacijenata zahteva operaciju, prevashodno starija deca zbog smanjenog kapaciteta remodeliranja. Efikasne hirurške metode uključuju elastične klinove i Kiršnerove igle. Buduća istraživanja bi trebalo da klasifikuju pacijente prema demografiji i tipu preloma kako bi se optimizovao tretman i procenili dugoročni ishodi.

**Ključne reči:** prelomi humerusa; prelomi ramena; dete; faktori rizika; ortopedske procedure; ishod lečenja

## Introduction

Fractures are a common occurrence in childhood, with approximately half of all children reaching adulthood without experiencing a single fracture (60% of girls and 49% of boys) [1]. Pediatric fractures often result in temporary activity restrictions and, in some cases, may lead to persistent functional limitations [2]. Proximal humerus fractures in children typically occur following a fall onto the shoulder or an outstretched arm. The most common mechanisms include falls from height, sports-related injuries, traffic accidents, and, less frequently, pathological fractures.

These fractures exhibit a considerable capacity for remodeling due to the proximal humeral growth plate, which contributes approximately 80% to the

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***Abbreviations***
CRIM – Closed Reduction Immobilization
CRIF – Closed Reduction Internal Fixation
ORIF – Open Reduction Internal Fixation

longitudinal growth of the humerus [3]. The proximal humeral physis closes between the ages of 14 and 17 years in females and between 16 and 18 years in males. Consequently, the closer a patient is to physeal closure, the lower the bone's remodeling potential [4].

The management of proximal humerus fractures in pediatric patients remains a topic of debate. According to Neer and Horwitz [5], grade I and II proximal humerus fractures in children and older adolescents are generally treated non-operatively. Immobilization is typically maintained for 3 to 4 weeks, with the duration determined by clinical and radiographic assessments of healing [6]. However, non-surgical management is not recommended for patients with open Neer and Horwitz grade I and II fractures, vascular injuries, or polytrauma [7].

Unlike in adults, where the criteria for surgical intervention are well established, the indications for operative treatment in pediatric patients remain controversial. Some trauma surgeons advocate for conservative management even in cases with significant displacement, citing the high remodeling potential of the proximal humerus epiphysis, which may obviate the need for surgery [8]. Conversely, it is argued that in children with less than two years of remaining growth, fractures with displacement exceeding 40° may not undergo sufficient remodeling, warranting surgical intervention [4].

Treatment decisions are primarily guided by the patient age, fracture displacement, and the bone's remodeling potential. Nonoperative management is generally preferred for younger patients and those with minimally displaced fractures, whereas surgical intervention is considered for older children with significantly displaced fractures.

An individualized approach is essential to determine the most appropriate treatment strategy. Various fixation methods are utilized in surgical management, including Kirschner wires [9], cannulated screws [10], elastic intramedullary nails [11], external fixators [12], and locking plates [13], with the latter typically reserved for patients nearing skeletal maturity [14]. However, surgical treatment carries potential risks, such as infection and neurovascular injury [15–17]).

This study aims to analyze the age and gender distribution of pediatric patients with proximal humerus fractures, identify the predominant mechanisms of injury, assess immobilization duration based on treatment modality, and evaluate the prevalence of surgical interventions.

## Material and Methods

This study was approved by the Ethics Committee of the Institute for the Health Care of Children and Youth of Vojvodina. Conducted retrospectively from 2016 to 2023, it included 249 pediatric patients (aged 0 to 17 years) of both sexes who sustained proximal humerus fractures and provided consent for participation. The only exclusion criteria were open fractures and incomplete medical records. Participants were categorized into two groups: the non-operative treatment group (n = 224) and the surgical treatment group (n = 25).

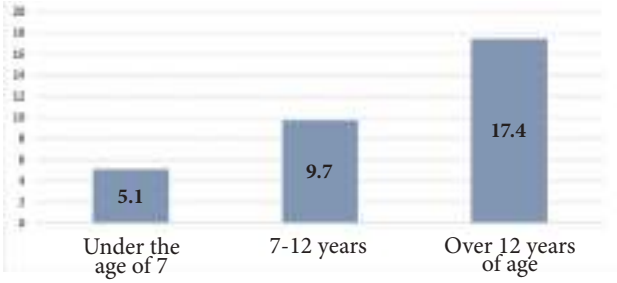
Among non-operatively treated patients, 127 (57%) were female and 97 (43%) were male. Fractures affected the left arm in 122 (54.5%) and the right arm in 102 (45.5%) cases. In the surgical group, 12 patients (48%) were female and 13 (52%) were male, with 15 (60%) sustaining fractures in the left arm and 10 (40%) in the right arm. The mean age of non-operatively treated patients was 9.12 years, whereas the mean age of operatively treated patients was 10.72 years.

Conservative treatment involved Desault's immobilization was following outpatient radiographic evaluation and fracture confirmation, with subsequent follow-up by an orthopedic surgeon. Patients requiring surgical intervention were admitted after diagnostic assessment and surgical indication confirmation. Procedures were performed under general anesthesia using one of the following techniques: Closed Reduction Immobilization (CRIM), Closed Reduction Internal Fixation (CRIF), or Open Reduction Internal Fixation (ORIF). Postoperatively, Desault's immobilization was applied when necessary, and all patients continued follow-up under orthopedic supervision.

All patients received treatment and follow-up at the same hospital, with clinical data recorded at each visit. Statistical analysis was conducted using the JASP software package. The Mann-Whitney test, Chi-square ($X^2$) test, and post-hoc tests were employed for data analysis.

## Results

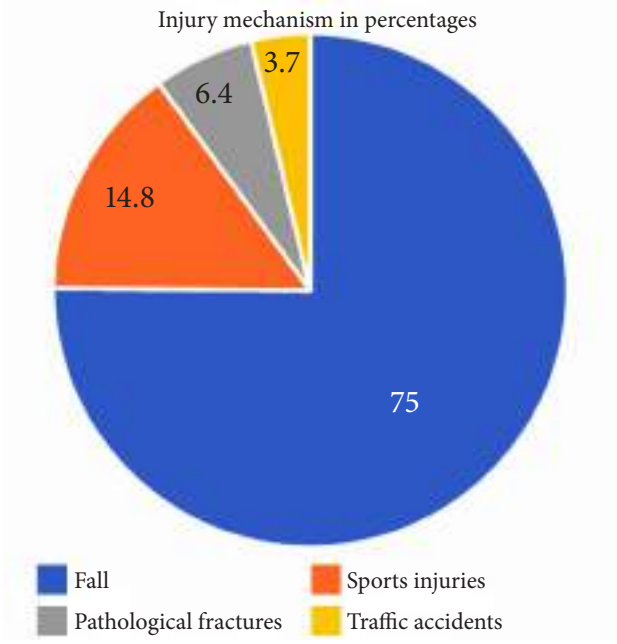
Of the 249 participants, 25 (10.04%) underwent surgical treatment. The proportion of patients requiring surgery increased with age: 5.1% of patients younger than 7 years, 9.7% of those aged 7-12 years, and 17.4% of patients older than 12 years underwent operative treatment (**Graph 1**). Among the 139 female participants, 12 (8.6%) underwent surgical treatment, while 13 (11.8%) of the 110 male participants required surgery. There was no statistically significant difference in surgical treatment rates between genders ($p > 0.05$).




**Graph 1.** Percentage of patients treated surgically by age group

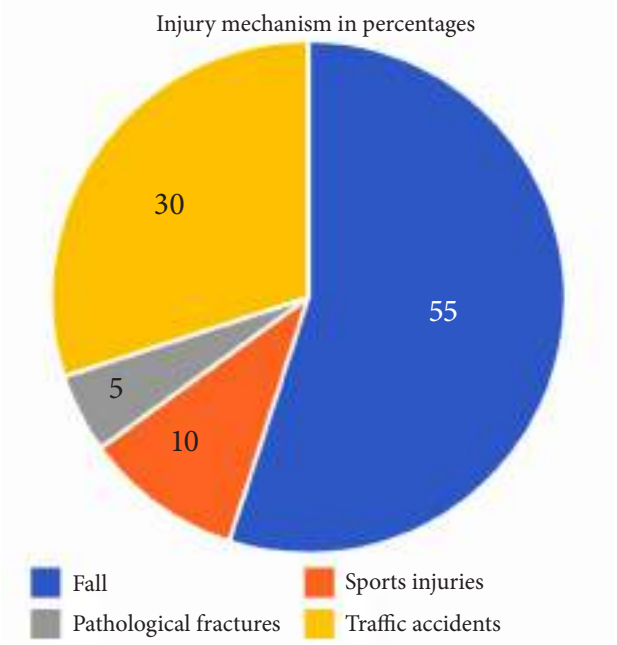
Among the 224 patients treated non-operatively, 127 (57%) were female, and 122 (54.5%) had fractures of the left arm. In the surgically treated group (n = 25), 12 (48%) were female, and 15 (60%) had fractures of the left arm. There was no statistically significant difference ($p > 0.05$) in gender distribution or affected limb between the surgical and non-surgical group, although left-sided fractures were more frequent in both.

In the non-operatively treated group, 38 (17%) patients were older than 12 years, 130 (58%) were aged 7-12 years, and 56 (25%) were younger than 7 years. In the surgically treated group, 8 (32%) were older than 12 years, 14 (56%) were aged 7-12 years, and 3 (12%) were younger than 7 years. While there was no statistically significant difference ($p > 0.05$) in the age distribution between the surgical and non-surgical groups, the surgical group had a higher proportion of older patients and a lower proportion of younger patients. In both groups, the majority of patients were in the 7-12 years age category.




**Graph 2.** Injury mechanism in the non-surgically treated group

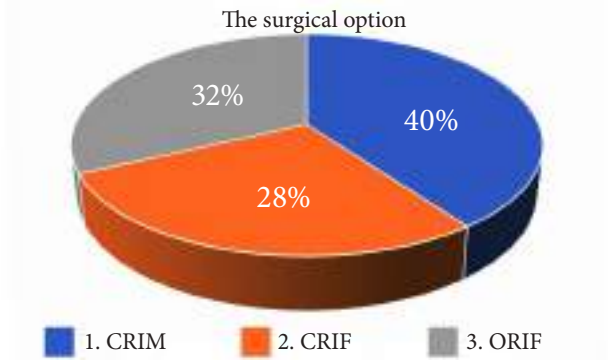
In the non-operatively treated group, the most common cause of fractures was falls (75%; n = 142), followed by sports injuries (14.8%; n = 28), pathological fractures (6.4%; n = 12), and traffic accidents (3.7%; n = 7) (**Graph 2**). In the surgically treated group, falls remained the most frequent cause (55%; n = 11), but traffic accidents were significantly more prevalent (30%; n = 6), followed by sports injuries (10%; n = 2), and pathological fractures (5%; n = 1) (**Graph 3**). A statistically significant difference ($p<0.05$) was observed in the mechanisms of injury between the two groups. Post-hoc tests indicated a highly statistically significant difference in the proportion of traffic-related fractures, which were markedly higher in the surgical group.




**Graph 3.** Injury mechanism in the surgically treated group

Among non-operatively treated patients, the average duration of immobilization was 22.3 days, whereas surgically treated patients required immobilization for an average of 34.3 days. The difference in immobilization duration was statistically significant ($p < 0.05$), with surgically treated patients requiring longer immobilization periods.

All non-surgical patients were managed in an outpatient setting, whereas surgically treated patients required hospitalization, with an average hospital stay of 4 days. Among the 25 surgically treated patients, Closed Reduction Immobilization (CRIM) was utilized for 10 patients, Closed Reduction Internal Fixation (CRIF) for 7 patients, and Open Reduction Internal Fixation (ORIF) was used for 8 patients (**Graph 4**). Of the 15 patients who underwent internal fixa-




**Graph 4.** Surgical technique used in the operated group

tion, 8 were fixed with elastic nails, 6 with K-wires, and 1 patient with a locking plate.

## Discussion

Upper extremity fractures are the most common fractures in children, accounting for approximately 80% of all pediatric fractures, with distal radius and supracondylar humerus fractures being the most frequent [18]. Proximal humerus fractures, however, are relatively rare, constituting about 2% of all fractures in children [19].

The optimal management of pediatric proximal humerus fractures remains controversial, with no clear consensus on indications for surgical treatment despite multiple proposals over the past 30 years [6, 8, 11, 12, 14]. In adults, approximately 15.7% of these fractures are managed surgically [20], whereas in children, due to open growth plates and the potential for remodeling, surgical intervention is less common. In our study, 10.04% of patients underwent surgery, aligning with previous studies reporting surgical rates between 10% and 17.3% [21, 22]. Kim et al. [23] found that older adolescents were twice as likely to undergo surgery compared to younger adolescents (19.8% vs. 8.5%, $p < 0.01$), a finding consistent with our study, where a significantly higher proportion of patients older than 12 years required surgery.

In our cohort, 8.6% of female and 11.8% of male patients underwent surgery, slightly higher than the 7% of boys and 5% of girls reported by Jakobsen et al. [18]. Despite this variation, both studies suggest a 40% higher likelihood of surgery in male children. Kim et al. [23] also observed a higher frequency of surgical treatment in boys (13.4% vs. 9.4% in girls). The increased rate of surgery in their study may be explained by the inclusion of only patients older than 10 years, involving group with a higher proportion of closed growth plates.

Although most patients in our study were treated non-operatively, 10 patients (4%) underwent closed reduction under general anesthesia without fixation, while 15 patients (6%) required surgical fixation. These findings are comparable with those of Hannonen et al. [19], who reported 1% undergoing closed reduction under general anesthesia and 8% requiring surgical fixation.

Our study found that 32% of surgically treated patients required open reduction, a lower percentage than the rates reported by Bahrs et al. [17] (52%), Pavone et al. [24] (61%), and Binder et al. [22] (47.5%). Bahrs et al. noted that periosteum or biceps tendon entrapment often prevents closed reduction. Pahlavan et al. [25] reported biceps interposition at the fracture site in 9.4% of cases, highlighting this as a common cause of failed closed reduction.

Among the 25 surgically treated patients in our study, 12 (48%) were female, and 15 (60%) had left arm fractures, closely aligning with Pavone et al. [24], who reported 46.1% female patients and 57.7% left arm injuries. Other studies report a similar gender distribution in surgical cohorts, ranging from 44% to 60.4% female patients [26, 27].

The average age of non-operatively treated patients in our study was 9.12 years, compared to 10.72 years for those treated operatively. Pavone et al. [24] reported an average surgical age of 12.8 years, while Canavese et al. [26] found 11.1 years, both consistent with our findings. Binder et al. [22] observed an average surgical age of 11.3 years and non-surgical age of 9.9 years, noting a statistically significant difference. These findings reinforce that older patients (over 12 years) are more likely to require surgery, whereas younger patients (under 7 years) rarely undergo operative treatment.

In our surgically treated group, 11 (55%) fractures resulted from falls, 2 (10%) from sports injuries, 1 (5%) from pathological fractures, and 6 (30%) from traffic accidents. These findings are comparable to Pavone et al. [24], who reported falls in 54%, sports injuries in 31%, and traffic accidents in 15% as primary mechanisms. Traffic accidents were statistically more frequent in the surgical group, likely because they cause more severe fractures requiring surgery. Additionally, older adolescents, who are at greater risk of traffic-related accidents, are more likely to have closed growth plates, necessitating surgical intervention similar to adults.

The average hospital stay for operatively treated patients in our study was 4 days, comparable to Pavone et al. [24], who reported 3.1 days.

Non-operatively treated patients were immobilized for an average of 22.3 days, whereas surgically treated patients required 34.3 days of immobilization. Hohloch et al. [27] reported average immobilization

duration of 3.69 weeks for conservatively treated patients, and 3.8 weeks for those treated with Kirschner wires. Similarly, Binder et al. [22] documented immobilization periods of 3 weeks in conservatively treated patients and 3.1 weeks in surgically treated patients. These findings indicate that surgical patients require longer immobilization periods, likely due to greater fracture severity, whereas milder fractures heal faster with conservative treatment.

Among the 15 patients who underwent internal fixation, 8 (53%) were treated with elastic nails, 6 (40%) with Kirschner wires, and 1 patient (7%) with a locking plate. Binder et al. [22] predominantly used Kirschner wires (87.5%), locking plates (7.5%), screws, and external fixators (2.5% each). While Kirschner wires showed favorable outcomes, other studies [28] also highlight with the effectiveness of elastic nails. This underscores the need for further comparative research to determine the optimal fixation method, considering patient-specific factors. A standardized treatment algorithm could aid surgeons in selecting the most appropriate technique.

Several limitations must be acknowledged. As a retrospective study, detailed longitudinal follow-up was not possible. Additionally, the small surgical cohort (n = 25) reduces the statistical power and reliability of our findings. The broad categorization of injury mechanisms was another limitation – future studies should subdivide injury types to better identify risk factors for proximal humerus fractures in children. Furthermore, our study did not assess long-term functional outcomes. A prospective study evaluating functional recovery (e.g., Constant score at one year post-injury) would provide a more comprehensive understanding of treatment efficacy. These limitations underscore the need for cautious interpretation of the study results and highlight the importance of further research to address these gaps.

## Conclusion

Proximal humerus fractures occur equally in both sexes, with the highest incidence in children age 7 to 12 years. While no significant differences in age or gender distribution were observed among surgically treated patients, older children were more likely to undergo surgery, likely due to growth plate closure and reduced bone remodeling capacity. Falls were the most common injury mechanism across all patients, whereas traffic accidents were significantly more frequent among surgically treated patients, reflecting the greater severity of these fractures.

Surgical patients also required longer immobilization, further indicating higher fracture severity. Approximately 10% of children required surgical intervention, with elastic nails and Kirschner wires proving effective treatment options.

To optimize management, fractures should be classified using the Neer-Horowitz system. Future research should focus on longitudinal studies assessing functional outcomes through standardized shoulder function tests, which would help refine treatment strategies and improve clinical decision-making for pediatric proximal humerus fractures.

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# GENDER DIFFERENCES IN EXPOSURE TO HAND TRAUMA

# *RAZLIKE MEĐU POLOVIMA U IZLOŽENOSTI POVREDAMA ŠAKE*

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**Abstract**

**Introduction.** Hand injuries are among the most frequently treated conditions in plastic surgery. Suboptimal management can lead to prolonged healing, complications, significant morbidity, and severe disability. This study aimed to evaluate gender differences in the mechanisms, etiology, physical impairments, and post-traumatic stress symptoms associated with hand and forearm injuries following treatment. **Material and Methods.** This study included 101 patients with hand injuries treated at the Clinic for Plastic and Reconstructive Surgery, University Clinical Center of Vojvodina in Novi Sad, between 2020 and 2023. Data collected encompassed age, gender, education level, injury mechanism, hospitalization duration, defect reconstruction type, number of surgical procedures, and the Modified Hand Injury Severity Score. The Quick Disabilities of the Arm, Shoulder and Hand score and the Short Post-Traumatic Stress Disorder Rating Interview Score were calculated through telephone interviews. **Result**s. The mean Quick Disabilities of the Arm, Shoulder and Hand score was 37.8 in men, and 55.7 in women, while the mean Short Post Traumatic Stress Disorder Rating Interview Score was 8.6 in men and 12.1 in women. The mean Modified Hand Injury Severity Score was 47.1 in men and 43.2 in women. **Conclusion.** Women exhibited significantly higher Quick Disabilities the of Arm, Shoulder and Hand score and Short Post-Traumatic Stress Disorder Rating Interview Score scores than men, indicating greater physical impairments and an elevated risk of posttraumatic stress disorder following injuries. Additionally, circular saw injuries emerged as the most common injury mechanism.
**Key words:** Hand Injuries; Sex Factors; Stress Disorders, Post-Traumatic; Risk Factors; Injury Severity Score

**Sažetak**

**Uvod.** Povrede šake spadaju među najčešća hirurški lečena stanja u plastičnoj hirurgiji. Suboptimalni tretman može dovesti do produženog zarastanja, komplikacija, značajnog morbiditeta i teškog invaliditeta. Ova studija je imala za cilj da proceni polne razlike u mehanizmima povrede šake/podlaktice, etiologiji, fizičkim oštećenjima i simptomima posttraumatskog stresa nakon tretmana. **Materijal i metode**. U istraživanju je učestvovao 101 pacijent sa povredama šake lečen na Klinici za plastičnu i rekonstruktivnu hirurgiju Univerzitetskog kliničkog centra Vojvodine u Novom Sadu od 2020. do 2023. godine. Prikupljeni podaci obuhvataju starost, pol, nivo obrazovanja, mehanizam povrede, dužinu hospitalizacije, vrstu rekonstrukcije defekta, broj hirurških procedura i modifikovanu ocenu ozbiljnosti povrede ruke. Na osnovu telefonskih intervjua izračunali smo skor invaliditeta ruke, ramena i šake i skor za posttraumatski stresni poremećaj. **Rezultati.** Prosečan skor invaliditeta ruke, ramena i šake bio je 37,8 kod muškaraca i 55,7 kod žena. Slično tome, srednja ocena, skor za posttraumatski stresni poremećaj, bila je 8,6 kod muškaraca i 12,1 kod žena; srednja vrednost modifikovani skor povrede šake bila je 47,1 kod muškaraca i 43,2 kod žena. **Zaključak.** Studija pokazuje da žene imaju značajno viši skor invaliditeta ruke, ramena i šake i skor za posttraumatski stresni poremećaj od muškaraca, što ukazuje na veći broj fizičkih oštećenja i povećan rizik od posttraumatskog stresnog poremećaja nakon povrede. Pored toga, zapaženo je da je najčešći mehanizam povređivanja cirkularom.
**Ključne reči**: povrede šake; pol; post traumatski stresni poremećaj; faktori rizika; ocena težine povrede

## Introduction

The hand plays a vital role in both daily activities and occupational tasks, facilitating motor functions and refined sensory processes essential for object recognition and manipulation. Hand injuries are among the most common traumatic conditions, significantly affecting quality of life and posing substantial medicolegal challenges [1]. These injuries encompass a wide spectrum, including lacerations, cuts, crush injuries, amputations, sprains, infections, fractures, and burns [2]. While rarely life-threatening, these injuries can lead to considerable morbidity and functional impairment. Individuals with visible scarring or deformities may experience feelings of shame, leading them to conceal the affected hand in social settings [3].

According to a 2019 report by Serbia's Ministry of Labour, upper limb injuries account for 44.91% of

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***Abbreviations***

| | |
|---|---|
| RTW | – return to work |
| QoL | – quality of life |
| PTSD | – post-traumatic stress disorder |
| QuickDASH | – Disabilities of the Arm, Shoulder and Hand |
| SPRINT | – Short Post-Traumatic Stress Disorder Rating Interview |
| MHISS | – Modified Hand Injury Severity Score |

occupational injuries, predominantly affecting males (64.23%), with the highest incidence observed in individuals aged 46-55 years (28.33%) [4]. Hand injuries frequently disrupt routine tasks, delay return to work (RTW), and impose substantial financial burdens [5]. The severity and nature of the injury significantly influence recovery, functional independence, and overall quality of life (QoL), a multidimensional concept encompassing physical, psychological, and social aspects [6, 7].

Beyond physical impairment, traumatic hand injuries are associated with an increased risk of post-traumatic stress disorder (PTSD), affecting 8-24% of patients [8, 9]. If rehabilitation focuses solely on physical recovery, PTSD symptoms may go unrecognized and untreated [10, 11]. Studies highlight a strong correlation between the severity of hand trauma and PTSD symptom intensity [12]. Recognizing and addressing PTSD in treatment plans can enhance patient outcomes, as supported by evidence for the effectiveness of cognitive-behavioral therapy [13]. Gender differences further influence trauma response, with variations linked to factors such as age, socioeconomic status, and coping mechanisms [14].

This study investigates gender disparities in injury mechanisms, physical impairment, and PTSD symptoms among patients with hand trauma treated at the Clinic for Plastic and Reconstructive Surgery in Novi Sad.

## Material and Methods

This retrospective epidemiological study was conducted at the Clinic for Plastic and Reconstructive Surgery, University Clinical Center of Vojvodina, Novi Sad. It included patients with hand trauma who received treatment between January 2020 and November 2023. A total of 101 adult patients with hand injuries were enrolled in this study. Data were extracted from patient medical records and the institution's electronic database. Ethical approval was granted by the Ethics Committee of the University Clinical Center of Vojvodina (ID number 600-342, issued on December 22, 2023).

The study collected sociodemographic and clinical data, including gender, age, injury mechanism, duration of hospitalization, number of surgical procedures during hospitalization, type of surgical procedure, occurrence of injury in an occupational setting, time of injury, ability to return to work post-injury, health insurance status at the time of injury, education level, participation in occupational therapy, timing of occupational therapy, and patient's subjective assessment of improvement following treatment.

The Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) and the Short Post-Traumatic Stress Disorder Rating Interview (SPRINT) scores were calculated for each patient using standardized questionnaires via telephone interviews. Additionally, the Modified Hand Injury Severity Score (MHISS) was determined based on surgical reports.

The QuickDASH is an 11-item self-report questionnaire used to evaluate upper limb disability and related symptoms. Patients rate their difficulty performing various activities on a 5-point scale (1 = no difficulty, 5 = unable to perform). Scores are then converted to a 0-100 scale, with higher scores indicating greater disability. The QuickDASH has shown good reliability and validity in various populations with upper limb conditions, and it is often used to assess treatment outcomes and monitor changes over time.

The SPRINT is a 19-item structured interview designed for rapid screening and assessment of PTSD severity. It evaluated the four primary symptom clusters of PTSD: intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity. Each item is rated on a 5-point scale (0 = not at all, 4 = extremely), with the total score reflecting the overall PTSD symptom severity.

The MHISS is a comprehensive scoring system used to classify the severity of acute hand injuries. It accounts for multiple factors, including the type of injury (e.g., fractures, tendon or nerve damage), the specific anatomic structures affected, and complications such as open wounds or infections. Each component is assigned a weighted score, and the total score determines the injury severity category. The MHISS is commonly employed to guide treatment decisions, predicts functional outcomes, and facilitates research in hand trauma.

Based on the MHISS values, patients were categorized into four severity groups:

1. Mild – MHISS <20
2. Moderate – MHISS 21 – 50
3. Severe – MHISS 51-100
4. Major – MHISS >101

Statistical analyses were performed using JASP 0.17.1 software. Descriptive statistics, including arithmetic mean, median, and standard deviation, were used to summarize the data. The Kolmogorov-Smir-

nov Test of Normality was applied to assess the normality of data distribution. Comparison of variables between genders was conducted using Student's t-test and Mann-Whitney. A p-value of <0.05 was considered statistically significant.

## Results

The study included 101 patients, comprising 74 men and 27 women, with a mean age of 43.3±16.5 years. All patients underwent surgical treatment for hand trauma at the Clinic for Plastic and Reconstructive Surgery between January 2020 and November 2023.

Analysis of injury mechanisms revealed that the most common cause of injury was a circulating saw. A gender-based comparison showed notable differences in injury mechanisms **(Table 1).** Over 50% of male patients sustained injured from either a circulating saw or a knife, whereas over 55.5% of female patients were injured by a knife or glass. A Mann-Whitney U test confirmed a statistically significant difference in injury mechanisms between genders (p = 0.032).

The duration of hospitalization was slightly longer for women than for men; however, this difference was not statistically significant. The mean hospital stay was 3.3 days for men and 3.4 days for women. The majority of patients, regardless of gender, underwent a single surgical procedure, with direct suture being the most commonly performed intervention.

Non-occupational injuries account for 73.26% of cases in both genders. Following treatment, 76.28% of patients reported could the ability to return to their previous job, while 20.8% described their pain as mild. At the time of their injury, 91.1% of patients had health insurance.

Regarding the time of injuries, most male participants (44.6%) sustained their injuries in the morning (6:00 AM - 12:00 PM), whereas most female participants (40.7%) were injured in the afternoon (12:00 PM – 6:00 PM). Educational background analysis revealed that 61.4% of patients held high school diploma. Additionally, 58% of female participants held a college degree, compared to 42% of their male counterparts, highlighting a significant educational disparity between genders.

Post-operative rehabilitation data showed that all female patients (100%) underwent occupational therapy, compared 95.9% of male patients. The mean interval between immobilization removal and the initiation of occupational therapy was 13.9 days for men and 14.8 days for women. Subjective assessments indicated an average well-being improvement of 82.4% for men and 72.2% for women. More male patients (16) reported complete recovery compared to female patients (2).

A gender-based comparison of QuickDASH scores revealed significantly lower mean values in male patients (37.8) compared to female patients (55.7), with a highly significant p-value <0.001, indicating substantial differences in functional outcomes. Similarly, the SPRINT score was significantly lower in men (8.6) than in women (12.1), with a p-value of 0.003, suggesting notable differences in pain perception. In addition, over 58% of female patients had a SPRINT score exceeding 14. In contrast, the MHISS scores did not show significant differences between genders **(Table 2)**.

**Table 1.** Distribution of injury mechanisms between men and women

| Mechanism | Men | Women |
|---|---|---|
| Circulating saw | 27.1% | 7.4% |
| Knife | 22.9% | 14.8% |
| Glass | 17.6% | 33.3% |
| Metal | 12.1% | 11.1% |
| Chainsaw | 6.7% | 7.4% |
| Axe | 1.3% | 3.7% |
| Traffic accident | 1.3% | 11.1% |
| Industrial machine | 8.1% | 7.4% |
| Grinder | 2.7% | 0% |
| Blender | 0% | 3.7% |

**Table 2.** Gender differences in DASH, SPRINT, and MHISS scores

| Score | Men | Woman | p |
|---|---|---|---|
| QuickDASH | 37.8 ± 18.2 | 55.7 ± 21.4 | <0.001 |
| SPRINT | 8.6 ± 6.3 | 12.1 ± 5.8 | 0.003 |
| MHISS | 47.1 ± 15.1 | 42.2 ± 17.6 | 0.3 |

**Table 3.** Gender differences in QuickDASH and SPRINT scores for specific groups of MHISS classification

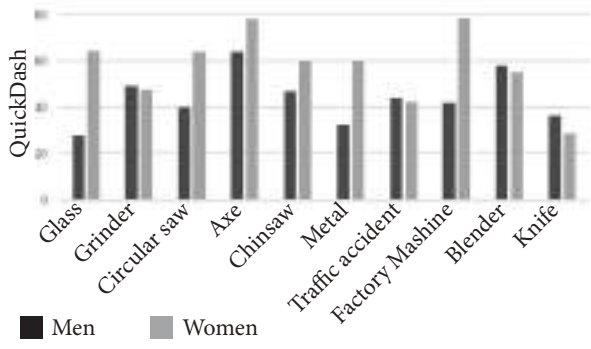
| MHISS group | Mild | Moderate | Severe | Major |
|---|---|---|---|---|
| Men | 2 | 46 | 26 | / |
| Women | 1 | 18 | 8 | / |
| QuickDASH (men) | 25 ± 9.2 | 36.2 ± 18.2 | 41.6 ± 18.2 | / |
| QuickDASH (women) | 68 | 52.3 ± 24.5 | 61.7 ± 12.3 | / |
| SPRINT (men) | 7 ± 4.2 | 7.3 ± 5.4 | 11.1 ± 7.3 | / |
| SPRINT (women) | 11 | 11 ± 5.9 | 14.9 ± 5.4 | / |
| p (QuickDASH) | / | 0.005 | 0.007 | / |
| p (SPRINT) | / | 0.02 | 0.193 | / |

Further classification of patients based on MHISS values yielded the following results **(Table 3)**:

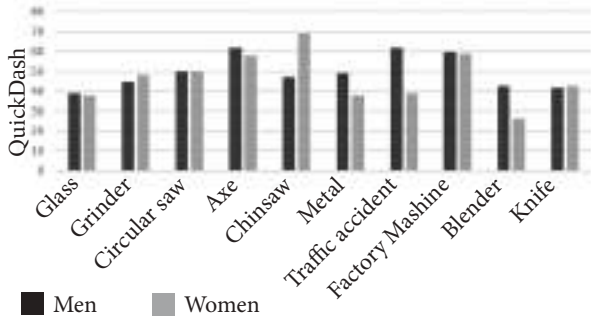
1. **Mild group** – Due to the small sample size (2 men and 1 woman), statistical significance between genders could not be determined.

**2. Moderate group** – The QuickDASH score was significantly lower in male patients (36.2) than in female patients (52.3), with a p-value of 0.005. Similarly, the SPRINT score was significantly lower in men (7.3) than in women (11), with a p-value of 0.02.

**3. Severe group** –The QuickDASH score was statistically significantly lower in men (41.6) than in women (61.7), with a p-value of 0.007. However, the SPRINT score did not show a statistically significant difference (p = 0.193).



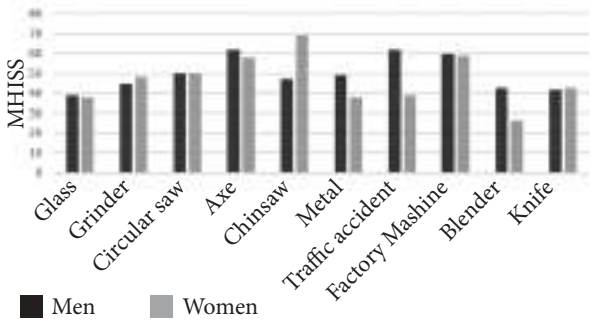

**Graph 1.** QuickDASH score in correlation with mechanism/tool of injury




**Graph 2.** SPRINT score in correlation with mechanism/tool of injury

**4. Major group** – No patients met the criteria for this group; thus, gender-based comparisons were not possible.

The following graphs illustrate the correlation between average QuickDASH, SPRINT, and MHISS scores and injury mechanisms **(Graphs 1, 2 and 3)**.




**Graph 3**. MHISS score in correlation with mechanism/tool of injury

## Discussion

Hand injuries have significant socioeconomic implications, medical costs, occupational therapy expenses, lost workdays, and challenges in the return-to-work (RTW) process. This retrospective study identified notable gender differences in QuickDASH and SPRINT scores, whereas MHISS scores showed no significant differences between men and women. These findings align with previous studies, such as those by Reitan et al. in Norway, where men exhibited less functional impairment in QuickDASH scores [15], and Aasheim and Finsen, who also reported lower QuickDASH scores among male patients [16].

Regarding PTSD symptoms, Ghițan et al. in Romania found no overall gender differences; however, women without permanent disability exhibited higher SPRINT scores than men [12]. Our results are consistent, with an average SPRINT score of 12.1 in women, and over 58% scoring 14 or higher, indicating a heightened PTSD risk. This aligns with Connor and

Davidson's recommendation that such patients undergo structured PTSD assessment [17].

The patients were categorized into four groups based on the Modified Injury Severity Score (MHISS) in order to compare the average QuickDASH and SPRINT scores between genders for each MHISS classification group (mild, moderate, severe, or major). We hypothesized that patients within one MHISS group would have a similar injury severity, and that comparing the average QuickDASH and SPRINT scores within one group would provide a more realistic insight into the actual differences between genders rather than *en masse* comparison. Our results revealed that most patients fell into the moderate and severe categories, consistent with findings by Marinković et al.[18].

The absence of gender difference in MHISS scores may be explained by the male-dominated sample, a trend observed by Marinković et al., where men tend to have higher MHISS scores due to injury types and severity. However, the higher QuickDASH and SPRINT scores among women in our study suggest that gender-sensitive rehabilitation strategies could enhance recovery, particularly given the increased likelihood of severe PTSD symptoms among female patients [18, 19].

Workplace-related injuries were more frequent among men (29.7%) than women (18.5%), mirroring prior research in occupational risk disparities. Men are more frequently engaged in high-risk, physically demanding occupations, increasing their likelihood of sustaining workplace injuries, as noted in studies on gender and occupational safety [20].

RTW emerged as a key socioeconomic factor post-injury, with 77% of men and 74% of women returning to their previous roles post-treatment. While Chu et al. found no significant gender effect on RTW in Taiwan [21], Laisné et al. reported that women in Canada initially faced poorer RTW outcomes, likely influenced by workplace conditions and gender-based social roles affecting injury management and recovery [22].

Our study, limited to hospitalized patients, may not fully reflect the broader population of hand trauma injuries, as highlighted by Nikolić et al., who reported that only a small fraction (1.6%) of such injuries require hospitalization [2]. Gender-based differences in injury mechanisms were evident: men were more frequently injured by circular saws in non-occupational settings, aligning with findings from Pantelić et al. Women, in contrast, were more commonly injured by glass, consistent with data from Gokhan et al. in Turkey [23, 24].

A gender-based pattern also emerged in injury timing; men were more often injured in the morning, likely during tool use, whereas women sustained injuries more frequently in the afternoon, potentially during food preparation. Kringstad et al. reported similar gender-related patterns in injury timing [25].

Although the average hospitalization duration was slightly longer for women (3.4 days vs. 3.3 days for men), this difference was not statistically significant. However, previous trauma care studies suggest that women generally experience longer hospital stays due to injury complexity and potentially different rehabilitation needs [26].

Most hand trauma cases required only one surgical intervention, a finding consistent with Momcilovic et al., indicating that initial surgical management is often sufficient. The effectiveness of early and precise surgical intervention minimizes the need for additional procedures, reducing patient burden and optimizing recovery timelines [27].

Future research should explore long-term psychological and functional recovery outcomes in hand trauma patients, consisting of gender-based differences in social support, socioeconomic factors, and access to mental health care. Lucas et al. advocate for routine PTSD assessments in hand trauma follow-ups, especially for women, to facilitate timely mental health interventions and improve post-injury outcomes [28].

## Conclusion

Our findings reveal distinct gender-based patterns in hand injury mechanisms: men predominantly sustained injuries from circular saws, whereas women were more frequently injured by glass. Although Modified Hand Injury Severity Scores did not show significant gender differences, women reported substantially higher functional disability (as measured by Quick Disabilities of the Arm, Shoulder and Hand) and more severe post-traumatic stress symptoms Short Post-Traumatic Stress Disorder Rating Interview compared to men. These results underscore the importance of integrating gender-specific considerations into the assessment and rehabilitation of hand trauma patients. Tailoring interventions to address these differences could improve patient outcomes. Further research is warranted to explore the biopsychosocial factors underlying these disparities, which may guide more effective prevention and rehabilitation protocols.

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# THREE-DIMENSIONAL SURFACE AREA OF THE ANTERIOR CRUCIATE LIGAMENT TIBIAL INSERTION, AND ITS CORRELATION WITH THE ANATOMICAL CHARACTERISTICS OF THE PROXIMAL TIBIA

# *TRODIMENZIONALNA POVRŠINA PRIPOJA PREDNJEG UKRŠTENOG LIGAMENTA NA GOLENJAČI I NJEGOVA KORELACIJA SA ANATOMSKIM KARAKTERISTIKAMA PROKSIMALNE GOLENJAČE*

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**Abstract**

**Introduction**. Precise positioning of the tibial tunnel is crucial for successful anterior cruciate ligament (ACL) reconstruction. By correlating the ACL attachment area on the tibia with tibial plateau dimensions measured on two preoperative standard radiographs, it is possible to determine the optimal drilling angle preoperatively. **Material and Methods.** This study examined 32 tibial specimens with ACL attachments obtained during total knee arthroplasty. Anteroposterior and lateral preoperative radiographs were used to measure tibial plateau dimensions. A 3D scan of the ACL attachment area, performed with a Personal HAptic iNTerface Mechanism Omni device, provided two new measurements: the ACL attachment surface area ($mm^2$) and its projection on the tibia ($mm^2$). **Results**. The average anteroposterior and medial-lateral diameters of the tibial plateau were 47.81 mm and 71.94 mm, respectively. The mean ACL attachment area was 142.4 $mm^2$, and the average projection area was 110.2 $mm^2$. Multiple regression analysis demostrated statistically significant correlations between tibial plateau dimensions and the ACL attachment area. Mathematical-statistical procedures yielded formulas for predicting the attachment surface area (P = 7.585 x AP - 0.179 x ML - 207.319) and its projection (P = 3.466 x AP + 1.261 x ML - 146.218) based on measured anteroposterior and medial-lateral diameters of the tibial plateau. **Conclusion**. Standard radiographic measurements of the tibial plateau allow for accurate prediction of the ACL attachment area. Combined with drill bit diameter, these data support individualized determination of the tibial tunnel drilling angle, enhancing surgical precision in ACL reconstruction.

**Key words:** Anterior Cruciate Ligament Reconstruction; Tibia; Orthopedic Procedures; Radiography; Correlation of Data

**Sažetak**

**Uvod**. Iako je položaj tunela u butnoj kosti u centru pažnje, ne sme se potceniti značaj preciznog pozicioniranja tunela u golenjači. Pronalaženjem veze između površine pripoja prednje ukrštene veze (LCA) na golenjači i dijametra platoa na standardnim radiogramima, omogućava se određivanje ugla bušenja platoa koristeći samo dva preoperativno načinjena standardna radiograma. **Materijal i metode.** Istraživanje je sprovedeno je na 32 platoa golenjače sa pripojem LCA uzete tokom totalne aloartroplastike kolena kod kojih su preoperativno izmerene dimenzije platoa golenjače. Trodimenzionalno skeniranje prostorne površine pripoja LCA na platou golenjače u odnosu na ravan zglobne površine golenjače izvršeno je korišćenjem uređaja Personal HAptic iNTerface Mechanism Omni. Dobijene su vrednosti površine ($mm^2$) i projekcije pripoja ($mm^2$) LCA na golenjači. **Rezultati**. Prosečna vrednost anteroposteriornog dijametra bila je 47,81 mm a mediolateralnog 71,94 mm. Prosečna površina pripoja LCA bila je 142,4 $mm^2$ a prosečna projekcija pripoja 110,2 $mm^2$. Analiza varijanse multiple regresije pokazuje da se merenjem oba dijametra može postići statistički značajna korelacija, te su načinjene formule za izračunavanje površine i projekcije pripoja na osnovu izmerenih vrednosti anteroposteriornog i mediolateralnog dijametra platoa golenjače. Površina pripoja može se predvideti pomoću formule P = 7.585 x AP-0.179 x ML-207.319 a projekcija pripoja formulom P = 3.466 x AP + 1.261 x ML-146.218. **Zaključak**. S obzirom na visoku korelaciju, moguće je predvideti površinu pripoja LCA na golenjači merenjem samo anteroposteriornog i profilnog dijametra platoa na standardnim radiografskim snimcima. Poznavanje površine pripoja prednjeg ukrštenog ligamenta i prečnika burgije omogućava određivanje ugla bušenja tunela u golenjači.

**Ključne reči:** rekonstrukcija prednjeg ukrštenog ligamenta; golenjača; ortopedske procedure; radiografija; korelacija

## Introduction

The anterior cruciate ligament (ACL) plays a crucial role in preventing anterior displacement of the tibia relative to the femur and maintaining normal knee kinematics [1]. ACL injuries most commonly occur during sports activities [2]. The increasing number of ACL reconstructions each year has height-

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***Abbreviations***

| | |
|---|---|
| ACL | – anterior cruciate ligament |
| CGAL | – The Computational Geometry Algorithms Library |
| AP | – anteroposterior |
| ML | – mediolateral |
| BMI | – body mass index |
| MRI | – Magnetic Resonance Imaging |
| P | – tibial insertion area |

ened interest among orthopedic surgeons in optimizing surgical techniques and achieving superior outcomes in restoring anterior knee stability [3].

The primary objective of ACL reconstruction is to restore knee stability throughout the full range of motion [4]. Over the past two decades, advancements in our understanding of the ACL anatomy and function have led to a shift from the traditional isometric tunnel placement to anatomical reconstruction. Improper tunnel positioning remains the most frequently cited cause of ACL reconstruction failure. While femoral tunnel placement has received significant attention, precise tibial tunnel positioning is equally critical [5, 6]. Understanding the geometric characteristics of the ACL insertion site, including cross-sectional and three-dimensional surface area, is essential for determining the ligament mechanical properties and optimizing reconstruction outcomes [7]. Since grafts only partially cover the anatomical footprint, identifying the most functional position within the tibial attachment is necessary. Recent studies have emphasized the role of tibial tunnel positioning in ensuring translational control and rotational stability following ACL reconstruction [8–11].

In approximately 78% of cases, the ACL tibial insertion is elliptical, while in 22% it is triangular [12, 13]. However, in ACL reconstruction, the tibial graft

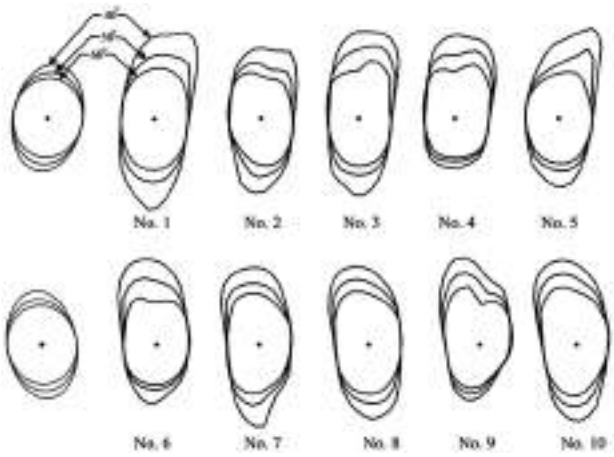



**Figure 2.** Different shapes and sizes of the tibial plateau aperture depending on the drilling angle: sagittal (40°, 50°, and 60°), transverse (10°), and a drill bit diameter of 10 mm. The correlation with the elliptical shape is also shown. (Adapted from: Milojević et al. [15])

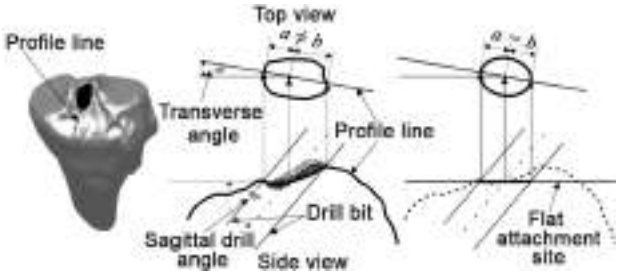


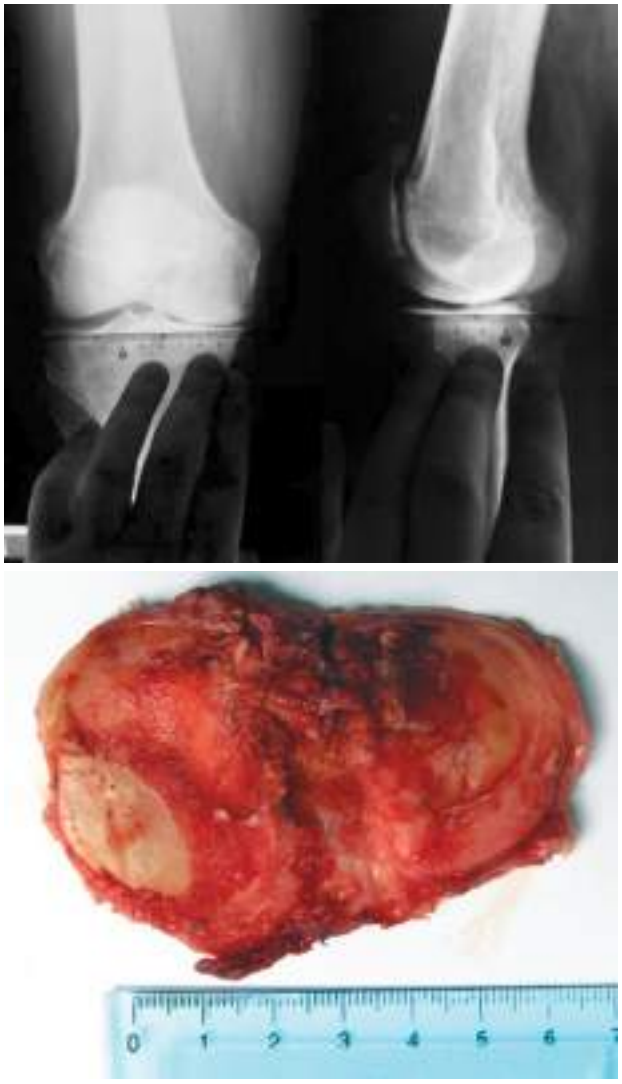

**Figure 1.** Tibial tunnel drilling; actual shape of the tunnel opening on the plateau created by the drill (center) and the elliptical opening on the plateau (right) if the ACL tibial attachment is assumed to be flat. (Adapted from: Milojević et al. [15]. Analysis of the tibial tunnel aperture area in ACL reconstruction. Med Pregl. 2016)

insertion site is often approximated as a circle or ellipse, which does not fully capture the graft's actual positioning. The size and location of the elliptical area of the tibial tunnel **(Figure 1)** are influenced by drill diameter and sagittal and transverse angles (the angle at which the tunnel intersects the tibial plateau) [14]. The tunnel opening on the tibia is analyzed as an ellipse formed by the intersection between the tibial articular surface and the tibial tunnel. However, since the tunnel opening on the tibia is not a perfect ellipse, patient-specific characteristics must be considered during reconstruction **(Figure 2).** Although the insertion surface is irregular, it is often approximated as an ellipse for simplicity. By establishing the relationship between the three-dimensional ACL tibial insertion area and the tibial plateau dimensions on standard radiographs, we propose a method for determining the optimal tibial drilling angle using only two standard preoperative radiographs.

## Material and Methods

Following approval from the Ethics Committee of the University Clinical Center of Vojvodina, a prospective study was conducted at the Clinic for Orthopedic Surgery and Traumatology in collaboration with the Faculty of Technical Sciences, University of Novi Sad. The study analyzed 32 tibial plateau specimens with intact ACL tibial attachments obtained during total knee arthroplasty. Standard AP and lateral radiographs with standard magnification were obtained preoperatively to measure tibial plateau dimensions **(Figure 3a).** Two numerical parameters were recorded: the anteroposterior (AP, in millimeters) and medial-lateral (ML, in millimeters) diameters.

Microdissection techniques were used to clearly define the ACL tibial attachment site **(Figure 3b).** A three-dimensional scan of the attachment area on the tibial plateau was then performed using the PHANToM



**Figures 3a and b. a.** Preoperative knee radiographs in two projections – AP (left) and lateral (right) – showing the AP (in mm) and ML (in mm) diameters of the proximal tibia. **b.** Tibial plateau with the ACL attachment.

Omni device **(Figure 4),** which allows precise determination of object position (three degrees of freedom along x, y, and z axes) and orientation (three rotational

**Figure 4.** PHANToM Omni haptic device

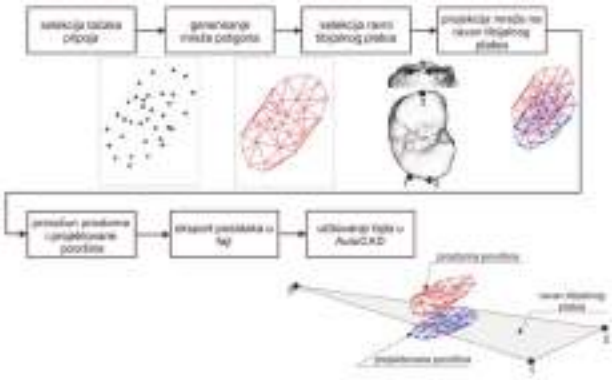


**Figure 5.** Model of the developed software solution

degrees of freedom). The device also provides force feedback in the x, y, and z directions, enabling the user to "feel" contact with virtual objects. This method yielded two additional numerical parameters: the three-dimensional surface area of the attachment ($mm^2$), and its projected area ($mm^2$) onto the tibial plateau plane.

A specialized software solution, developed in the C++, was used to generate the tibial insertion area, store collected data, and facilitate further analysis. The model of the developed software solution is shown in **Figure 5.**

The first step involves selecting the attachment points. Using the haptic device, the user selects reference points on the tibial surface, pressing a button to record each point's coordinates. The attachment area is computed using a mesh of triangular polygons, generated with the Delaunay_triangulation_2 class from the Computational Geometry Algorithms Library (CGAL).

To determine both the spatial area of the insertion and its projection onto the tibial plateau plane, three points defining the tibial plateau plane are selected using the same method. A second triangular mesh is then created as a projection onto this plane (the blue surface in **Figure 5**). The total spatial and projected areas of the ACL insertion are calculated as the sum of the individual triangular areas in each mesh.

The final step in the software solution is data storage. The calculated areas, along with the coordinates of the triangles and plateau plane points, are saved in a file for further analysis. The data can be imported into AutoCAD if needed.

## Results

The mean AP diameter was 47.81 mm, and the mean ML diameter was 71.94 mm. The mean ACL tibial insertion area was 142.4 $mm^2$, while the mean projected area was 110.2 $mm^2$. Three-dimensional scanning identified three distinct shapes of the ACL tibial insertion: triangular, oval, and irregular. Strong correlation was observed between the following parameter pairs: AP and

**Table 1.** Age, nutritional parameters, attachment dimensions, and statistical results in patients whose tibial plateau surfaces were analyzed

| | | SD | SE | min | max | CV | Confidence interval | | Skewness | Kurtosis | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 68.59 | 8.63 | 1.52 | 45.0 | 81.0 | 12.58 | 65.48 | 71.71 | -0.58 | -0.06 | 0.952 |
| Height | 167.1 | 8.73 | 1.54 | 152.0 | 189.0 | 5.22 | 163.9 | 170.24 | 0.68 | 0.40 | 0.572 |
| Weight | 84.22 | 12.19 | 2.16 | 60.0 | 110.0 | 14.48 | 79.82 | 88.62 | 0.26 | -0.64 | 0.371 |
| BMI | 30.15 | 4.76 | 0.84 | 23.4 | 41.6 | 15.80 | 28.43 | 31.87 | 1.41 | 1.33 | 0.024 |
| AP | 47.81 | 3.77 | 0.67 | 43.0 | 57.0 | 7.89 | 46.45 | 49.17 | 1.00 | 0.03 | 0.188 |
| ML | 71.94 | 5.15 | 0.91 | 65.0 | 85.0 | 7.16 | 70.08 | 73.79 | 0.93 | 0.61 | 0.341 |
| Footprint area | 142.4 | 38.95 | 6.89 | 62.2 | 238.9 | 27.35 | 128.4 | 156.46 | 0.32 | -0.16 | 0.086 |
| Footprint projection | 110.2 | 32.44 | 5.74 | 46.6 | 202.4 | 29.44 | 98.52 | 121.92 | 0.60 | 0.67 | 0.531 |

ML diameters (0.941), insertion area and its projection (0.915), insertion area and AP diameter (0.712), and insertion area and ML diameter (0.667). Moderate correlations were found between the projection and AP diameter (0.591), and the projection and ML diameter (0.579). Additionally, correlations were noted between tibial plateau dimensions and anthropometric characteristics: AP diameter and patient height (0.585), AP diameter and patient weight (0.418), ML diameter and patient height (0.619), ML diameter and patient weight (0.435), ACL insertion area and patient height (0.447), ACL insertion area and patient weight (0.466), and ACL insertion area and BMI (0.118) **(Table 1).**

Multiple regression analysis demonstrated that measuring both AP and ML diameters enables a statistically significant prediction of the ACL insertion area and its projection. The following mathematical models were derived:

ACL insertion area ($mm^2$): **P = 7.585 x AP - 0.179 x ML - 207.319**

Projected insertion area ($mm^2$): **P = 3.466 x AP + 1.261 x ML - 146.218**

When applying these formulas, differences between the measured and calculated insertion areas ranged from 2.478 to 54.933 $mm^2$, while for projections, they ranged from 0.636 to 57.953 $mm^2$. Regarding deviations between the computed and the measured insertion area, 26 patients (81.3%) had values within one standard deviation of the mean, while 6 patients (18.7%) were beyond this range. For the projected insertion area, 25 patients (78.2%) fell within one standard deviation of the mean, while 7 patients (21.8%) were outside this range. These findings suggest that the derived formulas allow for highly accurate predictions of the ACL insertion area and its projection.

## Discussion

One of the primary causes of early recurrent instability following ACL reconstruction is improper graft placement, particularly non-anatomical tunnel positioning [16]. While femoral tunnel malpositioning is more frequently implicated [17], poor tibial tunnel placement can also lead to recurrent instability. An anteriorly placed tibial tunnel can lead to graft impingement, graft failure, or reduced flexion, whereas a posteriorly placed tunnel may result in excessive laxity in flexion [18, 19]. Additionally, factors such as inadequate graft tension, insufficient graft size, and improper graft fixation can contribute to failure [20].

Since final graft positioning is determined by both femoral and tibial tunnel placement, there is a growing consensus that tunnels should be drilled within the native anatomical footprints rather than using conventional, non-anatomical techniques. This anatomical approach aims to restore stability and normal knee kinematics [21]. Conventional tunnel drilling methods typically reconstruct only about 57% of the native ACL tibial footprint [22], which, despite short-term postoperative success, does not fully restore knee biomechanics and may lead to degenerative changes over time. Anatomical ACL reconstruction, tailored to individual patient anatomy, seeks to address this limitation. Sadoghi et al. [23] reported that anatomical ACL reconstruction produces knee kinematics similar to those of an uninjured knee. Similarly, Bedi et al. [24] found that ACL fiber bundles contribute to distinct knee functions, and optimal graft placement is essential for stability and minimizing impingement. Their biomechanical study emphasized that the tibial tunnel should be centered within the native ACL tibial footprint, which is not merely the geometric center of the tibial plateau aperture but rather a patient-specific three-dimensional structure.

Arthroscopic identification of ACL footprints can be challenging. Siebold [25] proposed the use of an "insertion site table", which involves preoperatively measuring the anteroposterior diameter of the tibial plateau with a ruler. Rabuck et al. [26] suggested preoperative measurement of the sagittal MR images of the patellar tendon, ACL length, and tibial attachment. Quiles et al. [27] introduced a technique involv-

ing labeling and stereophotogrammetry that provides a detailed three-dimensional representation of the ACL insertion in vitro, including its raised borders, internal quarter-turn step-like structure, and indentations corresponding to intervals between fiber bundles. Wang and Lee's histological study showed that the ACL tibial insertion exhibits a medially eccentric staining pattern in the cartilage attachment area.

Standard AP and lateral radiographs are commonly used to assess graft positioning, but their accuracy is limited due to patient-specific bone morphology and limb position [28]. Computed tomography (CT), particularly with 3D or multiplanar reconstructions, offers the most precise assessment of graft placement but is constrained by high radiation exposure and cost. MRI can be an alternative, although artifacts from metal interference screws may obscure details. Additionally, specialized computer software can analyze tibial graft positioning using standard radiographs [29].

Despite the three-dimensional nature of ACL tibial insertion, it is often assessed using two-dimensional techniques. In surgical practice, the tibial tunnel aperture is typically represented as an ellipse, formed by the intersection of the tibial plateau and the tibial tunnel [30, 31]. However, this schematic simplification does for fully account for the actual bone geometry, resulting in a two-dimensional projection that underestimates the true three-dimensional attachment area. The intraoperatively created tibial tunnel aperture varies individually, and significantly differs from a perfect ellipse despite the common schematic representation.

The elliptical aperture area can be adjusted by modifying drill diameter and drilling angles to better approximate the true anatomical shape of the ACL tibial attachment [30]. A smaller sagittal drilling angle increases the attachment area, making it closer to the anatomical shape. Similarly, reducing the transverse angle produces an insertion area more representative of anatomical morphology. Therefore, preoperatively selecting the appropriate drill diameter and drilling angles could enhance ACL reconstruction outcomes. Since the ACL tibial insertion is three-dimensional, further improvement in reconstruction quality can be achieved through three-dimensional investigative methods [32].

By utilizing three-dimensional scanning with the PHANToM Omni device, we identified three distinct insertion shapes: triangular, oval, and irregular. While the triangular shape was most common, oval insertion areas were also observed [12]. The drill diameter and sagittal and transverse drilling angles influence the tibial tunnel aperture area during ACL reconstruction. Previous studies, such as Siebold et al. [33] described the ACL tibial insertion as "C"-shaped. However, this configuration was not observed in our sample, likely due to degenerative changes in our older patient population.

Regarding the ACL tibial attachment size, studies suggest that this area constitutes approximately 6% of the tibial plateau surface [33]. Our study aimed to predict the insertion area based on preoperative tibial plateau dimensions. We found that the mean ACL tibial insertion area in our sample was 142.4 ± 38.95 $mm^2$ (ranging from 62.2 to 238.9), while the mean projected area was 110.2 ± 32.44 $mm^2$ (ranging 46.6 to 202.4). A notable heterogeneity of the sample was observed, with large variations in insertion area, consistent with findings by other authors [34–36]. Siebold et al. [37] found that the ACL tibial insertion is the widest part of the ligament, measuring on average 114 ± 36 $mm^2$, while other authors reported average areas of 133.8 ± 31.3 $mm^2$ and 151.53 ± 28.95 $mm^2$. Kopf et al. [38] noted substantial variations in the ACL tibial insertion area and a significant but weak correlation between insertion size and BMI.

Our findings also indicate correlation between AP and ML diameters of the tibial plateau and patient height and weight, as well as correlation between the ACL tibial insertion area and patient height, weight, and BMI. Murawski et al. [30] demonstrated that ML diameter of the distal femur (bicondylar diameter) can predict the ACL femoral and tibial insertion size when MRI is unavailable. Our results also suggest correlations between the ML diameter of the tibial plateau and ACL insertion area, although not statistically significant, with a more significant correlation between AP diameter and insertion area.

Even with a perfectly centered tibial tunnel, there remains risk of impingement within the intercondylar notch. This risk depends on several factors, including ACL tibial insertion size, tibial tunnel diameter, and drilling angles. Studies indicate that when using a 10 mm graft with a drilling angle of 45° or less, 45% of knees are at risk of impingement, with 20% experiencing certain impingement. Therefore, when performing single-bundle anatomical tibial tunnel during ACL reconstruction, careful consideration of tunnel size and drilling angles is crucial to minimize the risk of intercondylar notch impingement [39].

## Conclusion

Based on the observed correlations, we developed a mathematical-statistical formula that can accurately predict the anterior cruciate ligament tibial insertion area in a high percentage of cases using only

two preoperative radiographic parameters – the anteroposterior and mediolateral diameters of the tibial plateau on anteroposterior and mediolateral views. By determining the anterior cruciate ligament insertion area and selecting the drill bit diameter, surgeons can optimize the drilling angle for the tibial tunnel.

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# INCIDENCE OF PERI-ARREST ARRHYTHMIAS ASSOCIATED WITH COVID-19

## *UČESTALOST PERIARESTNIH ARITMIJA TOKOM PANDEMIJE COVID-19*

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**Abstract**
**Introduction.** The COVID-19 pandemic has profoundly impacted all aspects of life, with increasing evidence highlighting its severe extrapulmonary effects. Notably, it has been implicated in the development of peri-arrest arrhythmias in patients with pre-existing cardiovascular conditions, underscoring the need for further investigation. The study aimed to evaluate the impact of the COVID-19 pandemic on the incidence of peri-arrest arrhythmias among hospitalized patients at the Institute of Cardiovascular Diseases of Vojvodina, all of whom had underlying cardiac pathology. **Material and Methods.** A retrospective observational study was conducted on patients hospitalized at the Institute from March 2018 to January 2022 for cardiovascular diseases. Risk factors, including hyperlipidemia, alcohol consumption, smoking, diabetes, and hypertension, were analyzed. **Results.** The findings revealed a significant increase in peri-arrest arrhythmias, particularly tachyarrhythmias, during the COVID-19 pandemic. Hypertension (80.6%) and hyperlipidemia (54.6%) were highly prevalent among the study population. In COVID-19-positive patients, tachyarrhythmias occurred were more frequent (31%) compared to the pre-pandemic period (11.4%), whereas the incidence of bradyarrhythmias remained unchanged. A strong association between arrhythmias and acute myocardial infarction was also observed in COVID-19-positive patients. **Conclusion.** The study confirms that the COVID-19 pandemic contributed to a heightened incidence of peri-arrest arrhythmias in hospitalized cardiac patients.
**Key words:** Arrhythmias, Cardiac; COVID-19; Risk Factors; Cardiovascular Diseases; Myocardial Infarction; Tachycardia; Bradycardia

**Sažetak**
**Uvod.** Pandemija COVID-19 značajno je uticala na sve aspekte života, a sve više dokaza ukazuje na ozbiljne vanplućne posledice. Posebno se ističe njen doprinos razvoju periarestnih aritmija kod pacijenata sa primarnim kardiovaskularnim oboljenjima, što zahteva dalje istraživanje. Cilj istraživanja bio je da se proceni uticaj pandemije COVID-19 na učestalost periarestnih aritmija kod hospitalno lečenih pacijenata u Institutu za kardiovaskularne bolesti Vojvodine, koji su imali primarno kardiološko oboljenje. **Materijal i metode.** Sprovedena je retrospektivna opservaciona studija na pacijentima hospitalizovanim u Institutu od marta 2018. do januara 2022. godine zbog kardiovaskularne patologije. Analizirani su faktori rizika kao što su hiperlipidemija, konzumacija alkohola, pušenje, dijabetes i hipertenzija. **Rezultati.** Studija je pokazala značajan porast periarestnih aritmija, posebno tahiaritmija, tokom pandemije COVID-19. Utvrđen je visok procenat hipertenzije (80,6%) i hiperlipidemije (54,6%). U COVID-19 pozitivnoj grupi tahiaritmije su se javljale češće (31%) nego u periodu pre pandemije (11,4%), dok je učestalost bradiaritmija ostala nepromenjena. Takođe, utvrđena je značajna povezanost između aritmija i akutnog infarkta miokarda kod COVID-19 pozitivnih pacijenata. **Zaključak.** Rezultati istraživanja potvrđuju uticaj pandemije COVID-19 na povećanu učestalost periarestnih aritmija kod hospitalizovanih pacijenata sa kardiološkim oboljenjima.
**Ključne reči:** aritmije; COVID-19; faktori rizika; kardiovaskularne bolesti; infarkt miokarda; tahikardija; bradikardija

### Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has introduced significant changes in medical practice, including a potential increase in peri-arrest arrhythmias. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), responsible for the pandemic, has infected over 776 million people worldwide. While primarily affecting the respiratory system, it also exerts substantial extrapulmonary effects, particularly on the cardiovascular system [1, 2]. This impact is likely attributed to the ability of SARS-CoV-2 to exploit the angiotensin-converting enzyme 2 (ACE2) receptor, which is abundantly expressed in key organs, in combination with the systemic hyperinflammatory response triggered by the infection [3].

Gojković et al. report that COVID-19 can induce both direct and indirect cardiovascular complications. Direct infection of cardiomyocytes, pericytes, and fibroblasts leads to myocardial injury with cardiotoxic effects, while hypoxia, microvascular damage of coronary blood vessels, endothelial cell infection, and widespread inflammation further exacerbate cardiovascular dysfunction [4].

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***Abbreviations***

| | |
|---|---|
| COVID-19 | – Coronavirus Disease 2019 |
| SARS-CoV-2 | – Severe Acute Respiratory Syndrome Coronavirus 2 |
| ACE 2 receptors | – angiotensin-converting enzyme 2 receptors |
| ARDS | – Acute Respiratory Distress Syndrome |
| ICVDV | – Institute of Cardiovascular Diseases of Vojvodina |
| PCR | – polymerase chain reaction |

Peri-arrest arrhythmias, defined as cardiac rhythm disturbances occurring immediately before or after cardiac arrest, and are classified into bradyarrhythmias and tachyarrhythmias [5].

Bradyarrhythmias (heart rate <50 bpm) may remain asymptomatic until they become critical, manifesting as altered consciousness, dyspnea, chest pain, hypotension, and oliguria [6]. Tachyarrhythmias (heart rate >100 bpm) are categorized based on their origin (supraventricular or ventricular) and QRS complex morphology (narrow and wide) [7, 8].

The progression of COVID-19 occurs in multiple phases, including the viral phase, the secondary replication phase, and culminating in severe stage marked by multisystem failure due to excessive cytokine release [9, 10]. Inflammatory cytokines, such as interleukin-6, can disrupt cardiac potassium and calcium channels, contributing to arrhythmogenesis [11]. Moreover, acute respiratory insufficiency and Acute Respiratory Distress Syndrome (ARDS), resulting from COVID-19-associated pulmonary infiltration, exacerbate hypoxia, further increasing the risk of arrhythmias [12].

Direct myocardial injury in COVID-19 patients is evidenced by markers such as NT-proBNP, cardiac troponin I, and high-sensitivity C-reactive protein, all of which are associated with an increased risk of arrhythmias. Additionally, electrolyte imbalance and early treatments such as hydroxychloroquine and azithromycin may further predispose patients to arrhythmic events by inhibiting potassium channels, thereby prolonging cardiac action potential and increasing risk of torsades de pointes [13, 14].

Early reports from Wuhan indicated that 44% of intensive care unit patients experienced arrhythmias, raising concerns about the between COVID-19 and peri-arrest arrhythmias.

This study aims to assess the impact of the COVID-19 pandemic on the prevalence of peri-arrest arrhythmias among patients hospitalized at the Institute of Cardiovascular Diseases of Vojvodina (ICVDV) following emergency admission, all of whom had pre-existing cardiovascular conditions.

*Hypotheses*

1. The prevalence of peri-arrest arrhythmias is higher among COVID-19-positive patients with pre-existing cardiovascular disease compared to similar patients hospitalized before the pandemic.

2. Cardiovascular risk factors, including hyperlipidemia, excessive alcohol consumption, smoking, diabetes, and hypertension, are associated with an increased prevalence of peri-arrest arrhythmias in COVID-19 positive patients.

3. Tachyarrhythmias occur more frequently than bradyarrhythmias in COVID-19 positive patients.

4. Myocardial infarction diagnosed alongside peri-arrest arrhythmias is more common in COVID-19-positive patients than in those with myocardial infarction before the pandemic.

5. Peri-arrest arrhythmias in COVID-19-positive patients are attributable to SARS-CoV-2 infection rather than to acute myocardial infarction, which is a known cause of peri-arrest arrhythmias.

## Material and Methods

This observational cohort study included 602 patients hospitalized at the ICVDV due to primary cardiovascular conditions following emergency admission between March 2018 and January 2022. Patient data were retrieved from the ICVDV information system.

The dataset included demographic information and cardiovascular risk factors such as alcohol consumption, smoking, hyperlipidemia, hypertension, diabetes mellitus, and the presence of a diagnosed myocardial infarction. Additionally, data on positive polymerase chain reaction (PCR) test results were collected for the experimental group.

Patients were categorized into two groups based on PCR test results:

– Experimental group consisting of 313 patients with a positive PCR test, hospitalized with a primary cardiovascular condition following emergency admission between March 15, 2020 and January 15, 2022.

– Control group comprising 289 randomly selected patients hospitalized with a primary cardiovascular condition following emergency admission before the COVID-19 pandemic, between March 15, 2018 and March 1, 2020. This group was included to minimize the potential misclassification due to false-positive PCR results, as some patients were diagnosed positive only after multiple tests.

Descriptive statistical measures, including mean, standard deviation, median, frequencies, and percentages, were applied. Comparisons of mean values between the two groups were conducted using the t-test for independent samples. Associations between categorical variables were assessed using the chi-square test for contingency tables or Fisher's exact test, where appropriate. Results were presented in both tabular and

graphical formats. A p-value of < 0.05 was considered statistically significant. Data analysis was performed using SPSS 17 statistical software.

## Results

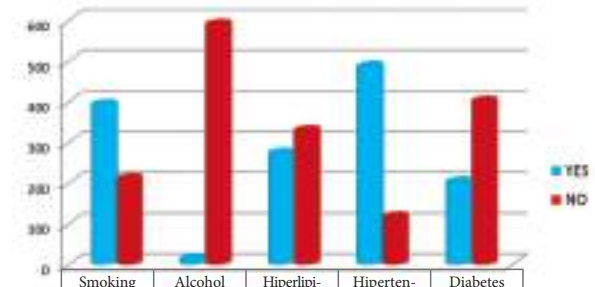
The study included 602 emergency-hospitalized patients with primary cardiac pathology, of whom 346 (59.1%) were men and 246 (40.9%) were women. The mean age was 68.24±11.99 years, with no statistically significant difference between genders. Demographic characteristics and cardiovascular risk factors, including smoking, alcohol consumption, hyperlipidemia, hypertension, and diabetes mellitus, are presented in **Graph 1.**

In regard to the risk factors, 34.9% of patients were smokers, 2.2% reported consuming alcohol, 54.6% had hyperlipidemia, 80.6% had hypertension, 33.6% had diabetes mellitus, 48.3% had a history of myocardial infarction, and 24.4% had pneumonia.

Peri-arrest arrhythmias were classified into bradyarrhythmias and tachyarrhythmias. Tachyarrhythmias were observed in 32.7% of patients, with atrial fibrillation (18.8%) and ventricular tachycardia (4.7%) being the most common. Bradyarrhythmias occurred in 7.2%, with third-degree AV block (4.2%) being the most frequent.

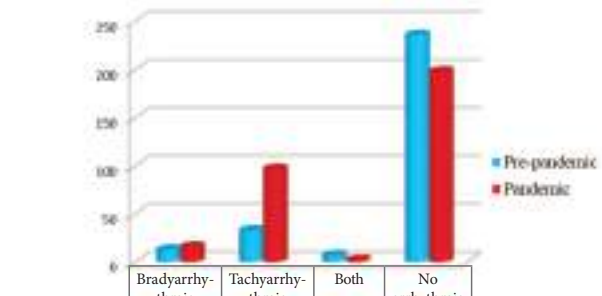
Patients were divided into two groups: pre-pandemic and COVID-19-positive. Tachyarrhythmias were significantly more frequent in COVID-19-positive patients (31%) compared to the pre-pandemic group (11.4%). Bradyarrhythmias showed similar prevalence in both groups, as shown in **Graph 2**.

A significant association was found between arrhythmia and COVID-19 status ($p < 0.0005$). The portion of patients without arrhythmias declined from 81.7% pre-pandemic to 63.3% during the pandemic. Bradyarrhythmias occurred in 4.5% pre-pandemic vs. 5.1% after the pandemic. Tachyarrhythmias increased from 11.4% pre-pandemic to 31% during the pandemic. The portion of patients with both bradyarrhythmias and tachyarrhythmias decreased from 2.4% pre-pandemic to 0.6% during the pandemic, as shown in **Graph 3.**



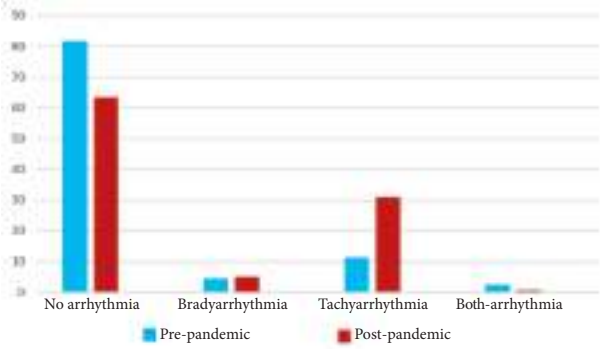

| | Smoking | Alcohol consumptio | Hiperlipi-demia | Hiperten-sion | Diabetes |
|---|---|---|---|---|---|
| YES | 392 | 13 | 273 | 485 | 202 |
| NO | 210 | 589 | 328 | 117 | 400 |

**Graph 1.** Overview of risk factors for the development of cardiovascular diseases




| | Bradyarrhy-thmia | Tachyarrhy-thmia | Both | No arrhythmia |
|---|---|---|---|---|
| Pre-pandemic | 13 | 33 | 7 | 236 |
| Pandemic | 16 | 97 | 2 | 198 |

**Graph 2.** Overview of incidence of peri-arrest arrhythmias in PCR-positive vs. PCR-negative patients




**Graph 3.** Arrhythmia prevalence trend pre- and during pandemic

A significant association was found between arrhythmias and AMI in COVID-19-positive patients ($p=0.004$): 53% of patients with AMI had no arrhythmias, 43.8% had bradyarrhythmias, 32% had tachyarrhythmias, and 0% had both bradyarrhythmia and tachyarrhythmia. These findings suggest that the increased incidence of arrhythmias during the pandemic was primarily due to COVID-19 infection rather than myocardial infarction.

The results highlight a significant impact of COVID-19 on the incidence of peri-arrest arrhythmias, particularly tachyarrhythmias. Additionally, hypertension and pneumonia emerged as key risk factors in this patient population.

## Discussion

Cardiac arrhythmias are a well-documented cardiovascular complication in patients with COVID-19. In a study of 138 COVID-19 patients, heart palpita-

tions were reported in 7.3% of cases [15]. In a retrospective study from Wuhan, China, found that 16.7% of hospitalized patients experienced cardiac arrhythmias, with a higher incidence in those in intensive care unit (ICU) patients (44.4%) compared to non-ICU patients (6.9%) [16, 17]. However, specific types of arrhythmias were not detailed.

Our study compared the incidence of peri-arrest arrhythmias before (March 2018 – March 2020) and during the pandemic (March 2020 – January 2022). The findings confirm a higher prevalence of peri-arrest arrhythmias during the pandemic, In another study, 16.7% of patients experienced arrhythmias, with a higher occurrence in ICU patients (44.4%) compared to non-ICU patients (6.9%) [18]. Guo et al. reported that 5.9% of patients developed sustained ventricular tachycardia or fibrillation [19].

Recent studies have investigated the types of arrhythmias associated with COVID-19 patients in the U.S.A. In a study of 393 patients in New York, 7.1% experienced atrial arrhythmias, while 0.3% had ventricular arrhythmias [20]. Critically ill patients had a higher incidence of arrhythmias, with 16.5% of ICU patients presenting with atrial arrhythmias [21]. Our study also confirmed that atrial fibrillation was the most frequent peri-arrest arrhythmia among critically ill patients.

Diverse arrhythmic manifestations have been observed in COVID-19 patients, including transient third-degree AV block, transient atrioventricular block, and pulmonary artery hypertension as part of ARDS [22, 23]. Tachyarrhythmias such as atrial fibrillation, atrial flutter, supraventricular tachycardias, and ventricular arrhythmias have also been reported [24]. Additionally, cases of multifocal ventricular tachycardia following ST-segment elevation and atrial flutter with second-degree AV block have been documented [16, 25, 26].

Atrial arrhythmias appear more frequent in COVID-19 patients compared to the general population, often occurring without a prior history of cardiac surgery, ablation, cardioversion, or antiarrhythmic drug use. A study from Columbia University during the pandemic peak in New York found that 31% of COVID-19 patients had atrial arrhythmias, although only 13% had a prior history of the condition [27]. The etiology involves ACE2 receptor alternations, inflammation, direct viral endothelial damage, and metabolic disturbances.

Atrial fibrillation is associated with worse outcomes in patients with acute respiratory illnesses, including ARDS and severe pneumonia. Increased mortality has been observed in patients with new-onset atrial fibrillation, particularly those requiring mechanical ventilation, where the incidence was 17.7% compared to 1.9% in non-ventilated patients. Moreover, some medications used for COVID-19 may contribute to QT interval prolongation, increasing the risk of torsades de pointes.

## Conclusion

This study assessed the impact of the COVID-19 pandemic on the prevalence of peri-arrest arrhythmias in patients hospitalized at the Institute of Cardiovascular Diseases of Vojvodina following emergency admission. All patients had pre-existing primary cardiovascular conditions. Among cardiovascular risk factors, hypertension emerged as a significant contributor to the increased incidence of peri-arrest arrhythmias in COVID-19 patients. Moreover, our results suggest that peri-arrest arrhythmias in COVID-19-positive patients were primarily attributable to the coronavirus rather than acute myocardial infarction, a well-established cause of such arrhythmias.

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# KNEE PROPRIOCEPTION OF YOUNG VOLLEYBALL PLAYERS AND BALLERINAS

# *PROPRIOCEPCIJA KOLENA MLADIH ODBOJKAŠICA I BALERINA*

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**Abstract**

**Introduction.** The aim of this study is to evaluate and analyze proprioception in adolescent girls. **Material and Methods.** This retrospective study included 39 girls aged 13 to 19 years, divided into two groups: 22 ballerinas and 17 volleyball players. Participants were tasked with consciously identifying a predetermined position of their lower leg without visual input. A digital goniometer was used to assess both the speed and degree of deviation from the targeted angle. **Results and Discussion.** Ballerinas demonstrated statistically significantly better proprioception in the left leg compared to volleyball players, in terms of both accuracy and intensity of the angular ascent ($p<0.05$). Volleyball players showed weaker and less precise performance in reproducing the left leg position, although their right leg proprioception was significantly better. In contrast, ballerinas exhibited no significant differences between the right and left leg in proprioception performance. **Conclusion.** Knee joint injuries are uncommon in ballerinas, likely due to their superior proprioception compared to volleyball players. Incorporating ballet-based techniques into volleyball and other athletic training programs may enhance proprioceptive ability and contribute to injury prevention.

**Key words**: Proprioception; Knee; Athletes; Sports; Dancing; Knee Injuries; Accident Prevention; Adolescent

**Sažetak**

**Uvod.** Cilj istraživanja predstavlja testiranje i analiziranje propriocepcije tinejdžerki. **Materijal i metode.** Retrospektivna studija je uključila dve grupe devojčica uzrasta od 13 do 19 godina. Od ukupno 39 ispitanica, 22 su balerine, a 17 odbojkašice, sa zadatkom da bez gledanja svesno odrede zadati položaj svoje potkolenice. Za eksperimentalni deo utvrđivanja brzine i stepena greške korišćen je digitalni goniometar. **Rezultati i diskusija.** U grupi balerina ustanovljena je statistički značajno bolja propriocepcija leve noge od grupe odbojkašica, kako u preciznosti, tako i u intenzitetu ugaonog uspona ($p < 0,05$). Odbojkašice su imale slabiju i manje preciznu realizaciju zadatog položaja leve noge, dok im je desnostrana propriocepcija bila značajno bolja. U grupi balerina ne postoje značajne razlike u testiranju obe noge. **Zaključak**. Povrede kolenog zgloba se veoma retko dešavaju među balerinama, jer imaju bolju propriocepciju od odbojkašica, te bi uvođenje baletskih tehnika u trening odbojke i ostalih sportova verovatno bilo efikasno u prevenciji povreda.

**Ključne reči:** propriocepcija; koleno; sportisti; sport; ples; povrede kolena; prevencija povreda; adolescenti

## Introduction

Proprioception, often referred to as the "sixth sense", describes the body's ability to perceive its position and movement in space [1]. Conscious proprioception facilitates complex motor tasks, while unconscious proprioception plays a key role in maintaining postural control during static (e.g., sitting and standing) and basic dynamic activities such as walking. Although the precise mechanism remains under debate, there is a general consensus that proprioceptive receptors are located within muscles, joints, ligaments and tendons [1, 2]. These receptors detect stimuli and transmit information to the central nervous system, which then coordinates appropriate motor responses [1, 2].

Women have a 2-8 times greater risk of knee injuries - particularly anterior cruciate ligament injuries – compared to men [3–11]. However, in the Republic of Serbia, men are more frequently injured and undergo surgical treatment for knee injuries [3–8]. Interestingly, knee injuries appear to be relatively rare among skaters, hockey players, ballerinas, and dancers [1, 4–8]. This raises important questions about whether Serbian sports programs are adequately implementing injury-prevention protocols and incorporating proprioception training to reduce non-contact injury risks.

It remains unclear how athletes perform hundreds of identical knee movements during training or competition without injury, while a seemingly identical movement may cause a serious injury. Although ballet is not widely practiced in Serbia, it is often (incor-

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***Abbreviations***

ACL – Anterior Cruciate Ligament
LCA – ligamentum cruciatum anterius
BMI – body mass index
UART – universal asynchronous receiver/transmitter
LESS – Landing Error Scoring System

rectly) perceived as safe with respect to knee injuries [9–11]. Each ballerina performs more than 200 jumps in a 1.5-hour training session, over half of which involve single-leg landing [9] - a particularly high-risk movement for ACL rupture. Despite this, ACL injuries are rare: reported in only 0.2-0.9% of ballerinas and 0.4% of competitive modern dances [9], compared to 1-8% in team sports [5, 10, 12].

Given these considerations, the aim of this study was to evaluate the accuracy of lower leg positioning as a measure of proprioception in adolescent females and to determine whether differences exist between girls actively engaged in volleyball versus ballet. We also reviewed the literature to explore whether elements of ballet training could be beneficially integrated into other sports such as volleyball [1, 13, 14].

## Material and Methods

The prospective study was conducted with approval from the Ballet School in Novi Sad and the "NS Volley Team" volleyball club in Novi Sad. The study included two groups of female adolescents aged 13 to 19 years. A total of 39 participants were enrolled through randomized selection: 22 ballerinas and 17 volleyball players. Inclusion criteria were female sex, age between 13 and 19 years, and absence of previous knee injuries or surgeries.

Parents have provided informed consent after being briefed on the study protocol, purpose, and measurement procedures. Both groups were matched for age, body mass index (BMI), physical activity level, and limb dominance. The average BMI was 22.3 kg/m$^2$ in the volleyball group, and 21.4 kg/m$^2$ in the ballet group. Limb dominance was right-sided in 31 participants and left-sided in 8.

An original digital goniometer device was used for proprioception assessment [1]. This microcomputer-based measurement and acquisition system consisted of three components: a sensor module affixed to the subject's leg, an electronic processing unit with a basic display, and a software application installed on a personal computer for data capture and storage.

The apparatus transmitted angle data every 200 milliseconds via a universal asynchronous receiver/transmitter (UART) protocol.

The device was metrologically validated in cooperation with the Laboratory for Metrology at the Department of Electrical Measurements, Faculty of Technical Sciences, University of Novi Sad [1].

Proprioception testing focused on the knee joints flexion at a target angle of 35°. Each participant was tested on both limbs in a standardized manner. Subjects lay prone in a quiet room without visual access to their legs or the device display. The examiner passively moved the lower leg from full extension to the target angle, which the participant was asked to memorize and maintain for 30 seconds before relaxing. Immediately afterward, the participant was instructed to actively reproduce the same angle. The protocol was repeated for both legs, with the order randomized.

The results were statistically processed. The basic parameters of the target and reproduced values of the angles, and the difference between the left and right leg in degrees are presented in tables. The verification of the non-parametric characteristics of the target and reproduced values of the angles is shown using $\chi^2$, Kolmogorov-Smirnov and t-test.

## Results

**Table 1** presents the basic parameters for the target (set) angles, achieved (realized) angles, and corresponding angular differences for the left and right knee of volleyball players.

Due to the relatively small sample size (N=17), the $\chi^2$ test could not confirm a definitive distribution pattern.

However, the Kolmogorov-Smirnov test indicated a potential normal distribution of the differences between the set and realized angles for the left leg ($p = 0.4294 > 0.05$), which was further supported by the $\chi^2$ test.

The Pearson correlation coefficient for the left leg among volleyball players was $r = 0.2025$, indicating

**Table 1.** Set and realized angles for volleyball players

| Values in degrees (°) | N | Mathematical expectation | Minimum | Maximum | Standard deviation |
|---|---|---|---|---|---|
| Left default | 17 | 37.6363 | 35 | 43 | 2.1940 |
| Left realized | 17 | 30.1818 | 25 | 35 | 3.1567 |
| Left (D-R) | 17 | 7.4545 | 0 | 15 | 3.4603 |
| Right default | 17 | 36.045 | 26 | 40 | 2.9354 |
| Right realized | 17 | 31.090 | 21 | 49 | 7.2500 |
| Right (D-R) | 17 | 4.9545 | -9 | 14 | 6.2828 |

**Table 2.** Angular ascent intensity of the left and right leg of female volleyball players

| Values in (°/msec) | N | Mathematical expectation | Minimum | Maximum | Standard deviation |
|---|---|---|---|---|---|
| Left | 17 | 0.040364 | 0.012 | 0.082 | 0.019261 |
| Right | 17 | 0.043955 | 0.011 | 0.081 | 0.021524 |

**Table 3.** Differences in the angular ascent value and intensity of a ballerina's legs

| Values in degrees (°) | N | Mathematical expectation | Minimum | Maximum | Standard deviation |
|---|---|---|---|---|---|
| Left (D-R) | 22 | 7.4545 | 0 | 15 | 3.4603 |
| Right (D-R) | 22 | 4.9545 | -9 | 14 | 6.2828 |
| Left leg intensity | 22 | 4.2727 | -5 | 9 | 3.1650 |
| Right leg intensity | 22 | 4.0909 | -3 | 10 | 3.9268 |

weak coordination and low accuracy in reproducing the set angle. In contrast, a moderate correlation as observed for the right leg ($r = 0.50995$), reflecting significantly better proprioceptive performance. The difference between the linear correlation coefficients for the left and right leg was statistically significant ($p = 0.00134 < 0.05$), clearly indicating superior right-leg proprioception in volleyball players.

Standard deviation (SD) analysis further supported this finding: SD of the angular error for the right leg ($s = 6.2828^o$) was greater than that of the left leg ($s = 3.4603^o$), suggesting the presence of a subgroup with highly refined right-leg coordination.

**Table 2** summarizes the basic parameters for the intensity of the angular ascent in both legs.

A statistically significant difference in the correlation between the set and realized angles and angular ascent intensity was found between the left and right legs ($p = 0.00023 < 0.05$), further indicating a proprioception imbalance favoring the right side.

For ballerinas, **Table 3** presents the differences in realized angles and angular ascent intensities for both legs. The $\chi^2$ test did not verify a definitive distribution. However, the Sign test revealed no statistically significant differences in accuracy between the left and right legs ($p = 0.6276 < 0.05$), indicating balanced proprioceptive performance.

The Sign test was also applied to compare angular distribution between volleyball players and ballerinas. A statistically significant difference was observed for the left leg ($p = 0.000022 < 0.05$), confirming superior left-sided proprioception for ballerinas. No significant difference was found for the right leg ($p = 0.662521 > 0.05$).

Regarding angular ascent intensity, ballerinas showed no statistically significant difference between their left and right legs ($p = 0.522431 < 0.05$). However, comparison between groups revealed a significant difference in left-leg angular ascent intensity ($p = 0.005578 < 0.05$), with ballerinas demonstrating higher values. Right leg ascent intensities were similar between the groups ($p = 0.135593 < 0.05$).

Finally, analysis of the correlation between angular error and angular ascent intensity showed the strongest negative correlation in ballerinas' left leg ($r = -0.3246$), indicating that greater angular ascent was associated with more accurate positioning. This correlation was significantly weaker in volleyball players ($r = -0.0155$; $p = 0.00877 < 0.05$).

For the right leg, no statistically significant difference was found between ballerinas ($r = -0.5640$) and volleyball players ($r = -0.4979$; $p = 0.1194 > 0.05$).

In summary, ballerinas demonstrated statistically significantly better proprioception in the left leg compared to volleyball players, both in terms of postural accuracy and angular ascent intensity.

## Discussion

In our previous studies, over 90% of patients undergoing surgical treatment for knee joint structures were aged between 16 and 35 years [3–8]. Due to the physical demands of elite sports and the overloading of immature knee joints, such injuries are increasingly observed even among adolescents [10, 15, 16]. Consequently, modern sports trauma literature emphasizes the study of etiology, identification of risk groups, risk factors, and injury mechanisms - particularly those related to the anterior cruciate ligament (ACL)- as understanding these elements is crucial for prevention [3–6, 10, 15, 16]. Athletes, especially professionals, are among the highest risk groups for ACL rupture [3–8, 10, 15, 16]. Accordingly, current training and rehabilitation protocols aim to minimize high-risk lower extremity movements associated with these injuries [10, 15–17].

Injury mechanisms are categorized into contact and non-contact types, with 60-80% of ACL ruptures occurring without contact with opposing players [1–3, 5, 15–17]. Direction changes and landing movements are the most frequent causes [1–3, 5, 15–17].

The prevalence of knee injuries varies across sports and regions. In Serbia, soccer players dominate most injury samples [3–8, 18], while in Nordic countries handball players and skiers are more commonly affected [12]. In the United States of America, rugby and basketball players predominate [19], and in Japan, basketball players, wrestlers, and skiers [16]. In contrast, knee injuries are rare among athletes such as hockey players, skaters, and ballerinas, due to minimal surface-footwear friction [2, 9, 17, 18]. In our prior research, only two ballet dancers and one hockey player underwent ACL surgery out of 6,000 patients [3–8, 18]. In the United States, professional dancers and ballerinas experience significantly fewer ACL injuries than athletes in team sports. In a study following 298 professional dancers over five years, only 12 ACL injuries were reported [9]. Notably, 92% of these injuries occurred during single-leg landings, and female dancers were at higher risk than their male counterparts [9]. These trends are attributed to superior coordination, refined jumping techniques, and skilled balance control. Injuries tend to occur late in the day and season, indicating muscle fatigue as a contributing factor [2, 9].

Ballerinas typically exhibit hypermobility, increased hip external rotation, and lumbar lordosis, which may compensate for injury risk [21]. The most common injuries are ankle overuse syndromes from excessive foot inversion during landings [22]. One study found that dancers engaged significantly more hip flexion during blind landing compared to controls, thereby preserving proprioception and reducing injury risk [23]. Gluteal muscle activation and reduced knee valgus angles during landing may further protect the ACL [24]. In our earlier studies [4–6, 25], female volleyball players were frequently injured during landings.

In volleyball, 32.4% of injuries result from landings, with 23.2% occurring during matches, possibly due to fatigue [2]. Muscle fatigue significantly impairs balance, proprioception, and jump performance, particularly in high-risk athlete groups [2, 9]. Knee extensor fatigue decreases jump height and forces reliance on compensatory muscles [2]. Based on the potential for ACL injury, Iranian authors [2] divided 40 female volleyball players by injury risk using the Landing Error Scoring System (LESS). A LESS score below 6 points indicates low risk, and above 6, high risk. They used a goniometer to test the participants to hold the set angle for five seconds with their eyes open firs, after which the examiner moved their leg to reach 60 degrees flexion with their eyes closed. Static balance was tested by standing on one leg, and the maximum height jump and balance maintenance during dynamic tests were also analyzed. Post-fatigue testing showed significantly worse static and dynamic balance, maximum jump height, landing quality, and proprioception in the high-risk group (LESS score 7.20 vs. 3.85 in low-risk group) [2].

Compared to volleyball players, ballerinas are more focused on technique during risky movements, while volleyball players prioritize gameplay actions such as scoring, defense, and rapid landings, often on an opponent's foot [18, 25]. Ballerinas also tend to have optimal body mass indices (BMIs below 25) [9], while volleyball players in low- and high-risk groups average BMIs 22.2 and 22.7 respectively [2]. The average BMI for female athletes is 22.4, and 23.6 for males [25]. The rarity of knee injuries among ballerinas is likely multifactorial, including precise movement patterns, daily training of standardized motor skills, and minimal influence from external factors such as opponents or playing surfaces [9, 25].

Preventive training – particularly involving plyometric drills, core stabilization, neuromuscular control, strength training and proprioceptive exercises – has been shown to significantly reduce ACL injury risk [9–11, 22, 24–26]. Such exercises improve knee flection, reduce valgus angles and sudden directional changes, and promote safe landings and body awareness. Exercise programs include single- and double-leg squats, pelvic lifts, bench and ball exercises, and controlled landings, and have demonstrated reductions in injury incidence by nearly two-thirds over three years [10, 15, 16, 24].

Conversely, studies by Czech and American researchers [19, 27] found no significant differences in balance between professional dancers and controls during single-leg stance tests (with or without turns, eyes closed). Ballerinas showed superior performance only after 10 full-body rotations, likely due to trained, repetitive movements. These authors emphasize vestibular, rather than proprioceptive dominance in maintaining posture and dynamic balance [19, 27]. Others attribute dancers' resistance to dizziness after pirouettes to vestibular rather than muscular adaptation [28].

However, other studies have reported better bipedal balance in ballerinas [11, 29]. Janura et al. [10] noted that single-leg balance requires greater attention and motor control. Turkish authors [30] observed improvements in vertical jump performance, flexibility, dynamic balance, coordination, and proprioception in ballet and modern dance students after a two-month core stabilization program. The exercise program designed for 45-60 minutes a day, three days a week [30]. Additional studies confirmed the effectiveness of neuromuscular control exercises involving the hips, knees, and ankles, which included standing,

running, stopping, jumping, and landing, with use of balls and unstable surfaces [31, 32].

Our study sample consisted of 39 adolescent girls: 22 ballerinas and 17 volleyball players. Since proprioception declines with age [1], examining a young cohort strengthens these findings. Moreover, as female sex is associated with higher ACL knee injury risk [2, 9, 10, 15], limiting the sample to girls enhances the specificity of our conclusions. All participants had similar age and BMI profiles and no prior knee injuries, eliminating confounding variables.

Proprioception is clinically measured using two standard methods [1, 2]: detection of passive motion or active reproduction of a passively set joint position, the latter being used in our study. Similar to our goniometric study, research has shown that ballet training enhances joint position sense [33]. Turkish authors using similar methods with upper limbs also reported greater accuracy of hand joint position among ballerinas than controls [34].

The clinical relevance of proprioception is further highlighted in postoperative rehabilitation. After ACL reconstruction, a return to sports is typically not recommended before six months due to proprioceptive deficits [1, 8, 35].

Interestingly, during the COVID-19 pandemic, rugby and soccer players in South Africa incorporated ballet techniques into training and reported improvements in flexibility, coordination, dynamic balance, and muscle endurance through exercises involving stretching, lunging, landing, turning, and dance movements [13, 14]. These findings support the potential for incorporating ballet techniques into volleyball and other sports to reduce injury risk.

Limitations include the small sample size and lack of access to advanced proprioception testing methods. The limited number of ballerinas reflects the underrepresentation of ballet in Serbia. We were also unable to compare additional anthropometric parameters. Future research should examine other sports and investigate why proprioception appears to be worse in the non-dominant left leg, particularly in volleyball players – possibly due to reflex dominance in right-handed athletes. Despite evidence suggesting no difference in reflexive muscle contraction between dominant and non-dominant leg [1], this aspect warrants further investigation. Our study included only adolescent females, and the scarcity of male ballet dancers in Serbia.

## Conclusion

In this study, young ballerinas demonstrated statistically significantly better proprioception of the left leg, both in terms of positional accuracy and angular ascent intensity. In contrast, volleyball players exhibited poorer coordination and less precise execution of the set angle with the left leg, while the right leg showed statistically significantly better proprioceptive performance. Among ballerinas, no statistically significant differences were observed in between the left and right leg in reproducing the set position. The rarity of knee injuries among ballerinas may be attributed to their superior proprioceptive abilities compared to volleyball players. These findings suggest that incorporating ballet-based techniques into volleyball and other sports training programs could have a preventive effect and potentially reduce the risk of lower extremity injuries.

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REVIEW ARTICLES
*PREGLEDNI ČLANCI*

# REVIEW OF CURRENT THERAPEUTIC APPROACHES FOR POLYCYSTIC OVARY SYNDROME

# *PREGLED AKTUELNIH TERAPIJSKIH PRISTUPA U LEČENJU SINDROMA POLICISTIČNIH JAJNIKA*

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Review article
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**Abstract**

**Introduction.** Polycystic ovary syndrome is a multifaceted endocrine disorder affecting 5-15% of women of reproductive age. This review aims to explore and synthesize current therapeutic strategies for managing polycystic ovary syndrome, emphasizing lifestyle modifications, pharmacological treatments, and emerging alternative therapies. A systematic literature search was conducted, focusing on randomized controlled trials, meta-analyses, and observational studies examining interventions that improve metabolic, reproductive, and psychological outcomes in women with polycystic ovary syndrome. **Current Therapeutic Strategies.** Lifestyle interventions, including weight management and regular exercise, are fundamental in enhancing insulin sensitivity and alleviating symptoms such as menstrual irregularities and hirsutism. Pharmacological treatments, including hormonal contraceptives, metformin, and anti-androgens, play a vital role in managing hyperandrogenism and promoting fertility. Additionally, emerging therapies, such as glucagon-like peptide-1 receptor agonists and herbal supplements, show potential in addressing metabolic dysfunction. Nutritional supplementation, particularly vitamin D, folic acid, and omega-3 fatty acids, has demonstrated benefits in improving both metabolic and reproductive outcomes. Complementary treatments, including acupuncture and herbal medicine, also hold promise but require further validation through robust clinical research. **Conclusion.** A personalized, multidisciplinary approach integrating lifestyle, pharmacological, and complementary therapies is essential for optimizing polycystic ovary syndrome management and improving patient outcomes.

**Key words:** Polycystic Ovary Syndrome; Insulin Resistance; Hyperandrogenism; Metformin; Inositol; Therapeutics

**Sažetak**

**Uvod.** Sindrom policističnih jajnika predstavlja složen endokrini poremećaj koji se javlja kod 5–15% žena u reproduktivnom periodu. Cilj rada je da istraži i objedini savremene terapijske pristupe u lečenju sindroma policističnih jajnika, sa posebnim fokusom na promene načina života, farmakološke tretmane i nove alternativne terapije. Sistematski pregled baza podataka obuhvatio je randomizovane kontrolisane studije, metaanalize i opservacione studije o lečenju sindroma policističnih jajnika. Odabrane studije bile su usmerene na intervencije koje imaju za cilj unapređenje metaboličkog stanja, plodnosti i mentalnog zdravlja kod žena sa sindromom policističnih jajnika. **Aktuelni terapijski pristupi u lečenju sindroma policističnih jajnika.** Promene načina života, poput regulacije telesne težine i redovne fizičke aktivnosti, ključne su za poboljšanje osetljivosti na insulin, kao i smanjenje simptoma poput neredovnih menstruacija i pojačane maljavosti (hirzutizam). Farmakološke strategije, uključujući hormonske kontraceptive, metformin i antiandrogene, igraju važnu ulogu u kontroli hiperandrogenizma i fertiliteta. Pored toga, inovativne terapije poput agonista receptora glukagonu sličnog peptida-1 receptora i biljnih dodataka pokazuju obećavajuće rezultate u tretiranju metaboličkih poremećaja. Suplementacija vitamina, posebno vitamina D i folne kiseline, kao i omega-3 masnih kiselina, donosi pozitivne efekte na metabolizam i plodnost. Alternativne terapije, kao što su akupunktura i biljni lekovi, takođe pokazuju potencijalne koristi, ali potrebna su dodatna istraživanja kako bi se potvrdila njihova efikasnost i bezbednost. **Zaključak.** U radu je naglašena važnost individualnog i integrisanog pristupa u lečenju sindroma policističnih jajnika, koji kombinuje promene načina života, farmakološke terapije i alternativne metode radi postizanja optimalnih ishoda za pacijentkinje.

**Ključne reči:** sindrom policističnih jajnika; insulinska rezistencija, hiperandrogenizam; metformin; inozitol; terapija

## Introduction

Polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome, is a prevalent and complex endocrine disorder affecting 5-15% of women of reproductive age. First identified in 1935 through symptoms such as menstrual irregularities, infertility, obesity, and hirsutism, it was initially termed

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***Abbreviations***

PCOS – polycystic ovary syndrome
NIH – National Institutes of Health
FSH – follicle-stimulating hormone
IR – insulin resistance
IL – interleukin
BMI – body mass index
LDL – low-density lipoprotein
FINS – exercise improved fasting insulin
CBT – cognitive behavioral therapy
COCs – combined oral contraceptives
SHBG – sex hormone-binding globulin
GLP-1 – glucagon-like peptide 1
VNS – vagus nerve stimulatio
taVNS – transcutaneous auricular vagus nerve stimulation

"secondary amenorrhea with infertility, obesity, and male-pattern hair growth" before being renamed PCOS in 1960. Diagnostic criteria have evolved over time. The 1990 NIH consensus requiring infrequent ovulation, hyperandrogenism, and exclusion of similar disorders, while the widely used Rotterdam criteria (2003) require two of the following: hyperandrogenism, oligo/anovulation, and polycystic ovaries [1, 2]. Based on these criteria, four phenotypes have been recognized: (1) HOP – hyperandrogenism, ovulatory dysfunction, and polycystic ovaries; (2) HO – hyperandrogenism and ovulatory dysfunction; (3) HP – hyperandrogenism and polycystic ovaries; and (4) OP – ovulatory dysfunction and polycystic ovaries without hyperandrogenism. These phenotypes underscore the syndrome's heterogeneity, making management complex [3]. Beyond reproductive dysfunction, PCOS is a polygenic, multifactorial disorder with metabolic, cardiovascular, and psychological impacts. Approximately 70% of affected women experience infertility due to anovulation. Elevated androgens contribute to hirsutism, acne, and insulin resistance, which increase the risk of obesity and type 2 diabetes. Genetic, environmental, and lifestyle factors play significant roles; for example, prenatal androgen exposure may predispose individuals to PCOS. Hormonal imbalances lead to the development of multiple antral follicles, causing menstrual irregularities and reproductive complications [4–7]. PCOS also has a significant psychological impact. Women with the condition are at an increased risk of anxiety, depression, and other mental health disorders, often exacerbated by symptoms such as hirsutism, infertility, and obesity [8].

### *Etiology of PCOS*

Polycystic Ovary Syndrome arises from a complex interplay of genetic predisposition, environmental factors, and lifestyle influences. While its exact cause remains unclear, prenatal exposure to excess androgens or environmental toxins has been implicated [9]. Genetic studies have identified multiple genes associated with hormonal imbalances, though further research is needed. Ovarian dysfunction is central to PCOS pathophysiology, but obesity significantly influences symptom severity. Enlarged subcutaneous adipocytes are associated with hyperandrogenism and visceral fat accumulation, reinforcing the link between obesity and hormonal dysregulation [3, 5, 6]. Theca cells in the ovaries overproduce androgens, while hormonal imbalances – including an elevated luteinizing hormone:FSH ratio, increased gonadotropin-releasing hormone pulse frequency, and low FSH – further disrupt follicular development, leading to ovulatory dysfunction and polycystic ovaries [10, 11].

### *Genetic Factors in PCOS*

Genetics play a major role in PCOS. The condition has a higher prevalence in certain ethnic groups, such as Spanish, Native American, and Mexican women, and family history increases risk [12]. Davies et al. identified a link between PCOS and cardiovascular risk in family members, with mothers of PCOS patients having twice the risk of hypertension and fathers a fourfold increased risk of stroke. Genes such as *INSIG2*, *MC4R*, and *TCF7L2* have been associated with insulin resistance and weight gain, with the latter contributing to an average increase of 1.56 kg/m² per allele [13]. Fica et al. further identified biochemical defects contributing to insulin resistance, such as impaired insulin receptor function and reduced PI3K activity, linking PCOS to an increased risk of type 2 diabetes and cardiovascular disease [14].

### *Hyperinsulinemia and Insulin Resistance*

Insulin resistance (IR) affects 50-70% of women with PCOS, regardless of body weight, due to post-receptor defects in insulin signaling. This leads to compensatory hyperinsulinemia, which stimulates theca cells to overproduce androgens, exacerbating symptoms such as hirsutism and acne. IR, combined with beta-cell dysfunction, elevates the risk of type 2 diabetes, hypertension, dyslipidemia, and cardiovascular diseases. Women with PCOS are also at increased risk for metabolic syndrome. Recent findings by Marotti et al. suggest that smoking further worsens cardiovascular risk in PCOS, highlighting the need for lifestyle interventions [14–16].

### *Role of Inflammation in PCOS*

Chronic low-grade inflammation is increasingly recognized as a key factor in PCOS pathogenesis. Elevated inflammatory markers – C-reactive protein, ferritin, necrosis factor-alpha, interleukin (IL)-6, and

IL-18 – impair insulin receptor function, contributing to insulin resistance. Altered iron metabolism, characterized by increased ferritin and transferrin levels and the HP2/HP2 genotype of haptoglobin, reduces anti-inflammatory capacity and exacerbates inflammation. This iron overload may further aggravate insulin resistance, increasing the risk of metabolic and cardiovascular complications [16].

This review aims to provide an in-depth analysis of available treatment options for PCOS. It evaluates lifestyle interventions, pharmacological treatments, and alternative therapies such as acupuncture and herbal medicine. The effectiveness, safety, and applicability of these approaches are compared to offer a practical guide for healthcare providers and patients in selecting the most suitable treatment strategies. Additionally, this review highlights areas where further research is needed to optimize PCOS management.

### *Current Therapeutic Strategies for PCOS*

The management of PCOS requires a personalized approach due to its heterogeneous presentation. Lifestyle modifications, pharmacological interventions, and emerging therapies are key components of treatment. Weight loss and increased physical activity significantly improve symptoms such as insulin resistance and menstrual irregularities. Pharmacotherapy includes hormonal contraceptives to regulate menstrual cycles and anti-androgens to reduce excess hair growth. Women seeking pregnancy may require fertility treatments such as clomiphene or assisted reproductive technologies. Additionally, alternative therapies like acupuncture and herbal medicine are being explored, though further research is needed to establish their efficacy [1].

### *Lifestyle Interventions*

Current guidelines emphasize the importance of lifestyle modifications for all women with PCOS to maintain a healthy weight and improve metabolic and reproductive outcomes. For those with excess weight, a 5-10% weight loss through a daily energy deficit of 500-750 kcal is recommended [17]. A Cochrane review of 15 trials demonstrated that lifestyle interventions significantly reduce weight, body mass index (BMI), and reproductive markers such as free androgen index, testosterone, and hirsutism, while lowering total cholesterol, low-density lipoprotein (LDL) cholesterol, and fasting insulin levels [18]. The findings align with a meta-analysis by Domecq et al., who found that lifestyle changes lower fasting glucose and insulin levels as effectively as metformin. Evan a modest weight loss (2-5%) has been linked to improvements in ovulation and menstrual regularity, while losses exceeding 5% enhance conception rates and reduce ovarian volume [19]. However, Pasquali et al. reported that even with over 5% weight loss, only one-third of women experienced full recovery from PCOS, with central adiposity and severe hyperandrogenism contributing to poorer outcomes [20]. This underscores the need for targeting interventions addressing insulin resistance and fat distribution, even in the absence of significant weight loss.

The 2018 PCOS guidelines recommend at least 150 minutes of moderate or 75 minutes of vigorous exercise per week for weight gain prevention, at least 250 minutes of moderate or 150 minutes of vigorous exercise per week for weight loss and prevention of weight regain, as well as strength training twice a week and minimizing sedentary behavior [21].

A comprehensive review of 18 trials (27 studies) by the year 2017 found that exercise improves fasting insulin (FINS), insulin resistance (HOMA-IR), cholesterol (TC, LDL-C), triglycerides (TAG), body composition (fat percentage and waist circumference), and aerobic fitness ($VO_2$max) compared to controls. Aerobic exercise specifically improves BMI, waist circumference, body fat, FINS, HOMA-IR, TC, TAG, and $VO_2$max. Resistance training reduces waist circumference and improves body composition, although it may decrease high-density lipoprotein-C and increase BMI. Combined aerobic and resistance training showed no significant impact on these markers. Recent reviews have confirmed that vigorous aerobic exercise can improve insulin resistance, body composition, and cardiorespiratory fitness. High-intensity interval training may improve insulin resistance and BMI, though evidence is inconsistent. Resistance training improves body composition and strength, and may also benefit androgen levels, although more research is needed. The impact of exercise type on reproductive function remains unclear [17].

Beyond diet and physical activity, adequate sleep and stress management play critical roles in PCOS management. Poor sleep and high stress exacerbate insulin resistance, complicating further PCOS symptoms such as irregular menstrual cycles, acne, and hirsutism. Behavioral interventions that promote better sleep, hygiene, and stress reduction techniques, such as mindfulness or cognitive-behavioral therapy, are gaining recognition as essential adjuncts to PCOS treatment. While lifestyle modifications are critical, they may not always be sufficient for symptom control, particularly in cases where obesity or insulin resistance is more severe, necessitating the addition of pharmacological therapy. Women with PCOS have a higher risk of depression and anxiety and report significantly lower quality of life than those without the condi-

tion. A meta-analysis found that CBT significantly reduces anxiety symptoms and improves quality of life, particularly regarding hirsutism. Some evidence also suggests CBT enhances patient adherence to treatment and increases pregnancy rates. However, there is limited evidence on its impact on BMI, menstrual health, infertility, social functioning, weight, and emotional well-being. More randomized, double-blind trials with larger sample sizes and extended follow-up periods are needed to clarify these effects [22].

***Medical treatment***

*Hormonal contraceptives*

When lifestyle modifications alone fail to adequately manage PCOS symptoms, pharmacological interventions are introduced, with combined oral contraceptives (COCs) being the first-line treatment. COCs regulate menstrual cycles, reduce hirsutism and acne, and suppress gonadotropin secretion, leading to increased sex hormone-binding globulin (SHBG) levels and reduced free androgen concentrations. Higher SHBG levels lead to fewer circulating free androgens, minimizing their effects on the skin and hair follicles. COCs also act directly on the hypothalamic-pituitary-ovarian axis, which helps regulate ovulation and menstrual cycles. Although various COC formulations exist, no specific combination has proven superior for PCOS treatment. However, the World Health Organization recommends COCs containing 35 μg of estrogen and cyproterone acetate for severe acne and hirsutism, though these formulations carry a higher thromboembolic risk and are considered second-line options. Women with metabolic syndrome or severe insulin resistance may not be ideal candidates for COCs, as they may exacerbate cardiovascular risks. Beyond COCs, progestin-only therapies may be considered in women who cannot tolerate estrogen, although they are less effective for hirsutism and acne. Other hormonal therapies, including clomiphene citrate (a selective estrogen receptor modulator) and letrozole (an aromatase inhibitor), are commonly used for ovulation induction in women with PCOS who pursue pregnancy. While clomiphene has traditionally been the first-line therapy, recent studies indicate that letrozole may offer higher ovulation and pregnancy rates, with improved maternal and fetal outcomes. Furthermore, combining letrozole with metformin or clomiphene citrate with metformin has been shown to yield similar follicle development without anti-estrogenic effects on the endometrium. Notably, the letrozole-metformin combination resulted in a higher pregnancy rate after the third intrauterine insemination cycle, suggesting that metformin and letrozole enhance ovarian response in moderately obese PCOS women resistant to clomiphene citrate [2, 23–26].

*Metformin's Role in PCOS Management*

Metformin, an insulin sensitizer, is widely used to address insulin resistance, a key driver of PCOS pathophysiology. It reduces hepatic glucose production, enhances peripheral glucose uptake, and improves insulin sensitivity, leading to lower insulin and androgen levels and improved ovulatory function. Although metformin's effects on menstrual regulation are mild to moderate, its impact on insulin sensitivity and androgen reduction is more pronounced. Recent guidelines suggest that combining metformin with COCs may provide greater benefits, particularly in overweight or obese women with PCOS, by simultaneously improving hyperandrogenism and metabolic parameters. Metformin has also been shown to reduce anti-Müllerian hormone levels, a marker of ovarian dysfunction, indicating potential benefits for ovarian reserve and function. However, while metformin enhances metabolic and reproductive outcomes, it is less effective than COCs for treating acne and hirsutism. Common adverse effects include gastrointestinal disturbances (e.g., diarrhea, nausea, abdominal discomfort), which may limit tolerability in some patients. Contraindications include severe renal impairment and metabolic acidosis, necessitating careful patient selection. Emerging research explores metformin in combination with other agents, such as GLP-1 receptor agonists (e.g., liraglutide and semaglutide), which have shown promising effects on weight loss and insulin resistance, areas where metformin alone may be insufficient [10, 27–30].

*Antiandrogens and Combination Therapies*

Antiandrogens play a crucial role in managing hyperandrogenism in PCOS, particularly for symptoms such as hirsutism and acne. Spironolactone and flutamide function by blocking androgen receptors, reducing the effects of elevated androgen levels. Spironolactone is the most commonly prescribed due to its dual role as both an antiandrogen and a diuretic, which may help alleviate fluid retention in PCOS. However, potential adverse effects, including gynecomastia and hyperkalemia, necessitate regular monitoring. Another option, finasteride, a 5-alpha-reductase inhibitor, reduces the conversion of testosterone to dihydrotestosterone, a potent androgen implicated in hair growth and acne. While androgens are effective in symptom relief, they are frequently used in combination with COCs to enhance therapeutic outcomes. Despite their widespread use, high-

quality studies evaluating antiandrogens in PCOS remain limited, and further research is needed to establish their long-term safety profiles [31, 32].

*Emerging Therapies: Semaglutide and Tirzepatide*

Recent advances in PCOS treatment have focused on medications that target weight management and insulin sensitivity. Semaglutide, a GLP-1 receptor agonist, has demonstrated significant weight loss and metabolic benefits in women resistant to lifestyle interventions. In a study by Carmina and Longo, three months semaglutide therapy resulted in significant reductions in BMI, fasting glucose, insulin levels, and HOMA-IR (a marker of insulin resistance). Notably, nearly 80% of obese women with PCOS achieved at least a 5% weight loss, leading to improved insulin sensitivity and glucose regulation. Compared to metformin, semaglutide exhibited superior efficacy with minimal side effects. Another promising agent, tirzepatide, recently Food and Drug Administration-approved for diabetes management, is being explored for PCOS treatment. Tirzepatide acts via a dual mechanism, targeting glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, resulting in substantial weight loss and improved insulin sensitivity. Additionally, tirzepatide has been associated with fewer gastrointestinal side effects compared to traditional GLP-1 receptor agonists. However, further clinical trials in PCOS populations are needed to confirm its effectiveness and safety in this context [33, 34].

*Surgical Approaches*

For PCOS patients unresponsive to first-line infertility treatments such as clomiphene citrate or gonadotropins, surgical interventions like ovarian wedge resection and laparoscopic ovarian drilling present viable alternatives. Clomiphene resistance affects approximately 15–25% of anovulatory patients, necessitating alternative strategies. Ovarian wedge resection, first described by Stein and Leventhal in 1935, initially demonstrated pregnancy rates of 81–87%. However, concerns regarding postoperative adhesion led to a decline in its use after the 1960s, as medical therapies improved. Between 1935 and 1983, the cumulative pregnancy rate following resection was 59%. Modern surgical advancements, including microlaser and laparoscopic electrocautery drilling, have improved pregnancy rates to 60-65%, though adhesion rates remained highly variable (19-86%).To mitigate adhesion risk, minimally invasive techniques that preserve ovarian stroma have been developed. One promising approach involves vertical resection near the utero-ovarian ligament after exteriorizing the ovary, achieving adhesion rates as low as 11% and pregnancy success rates of up to 90%. Despite its historical decline, ovarian wedge resection – particularly via mini-laparotomy – remains a valuable option for women unresponsive to standard ovulation induction. It offers high fertility success rates, short hospitalization, and reduced adhesion risk [25, 35–38].

*Nutrient Deficiencies and Complementary Therapies in PCOS*

Women with PCOS frequently exhibit deficiencies in essential vitamins and minerals, which may contribute to both psychological symptoms (depression and anxiety) and physiological disturbances (insulin resistance, infertility, metabolic dysfunction). Nutrient supplementation, when integrated with lifestyle and pharmacological interventions, may enhance symptom management and long-term outcomes [39].

Vitamin D enhances insulin sensitivity, particularly at low daily doses, and may improve pancreatic beta-cell function. While its role in glycemic control is well-documented, its effects on lipid profile, androgen levels, and body weight remain inconclusive and require further research [40, 41].

Inositols, particularly Myo-inositol and D-chiro-inositol, play a key role in insulin signaling and glucose metabolism in ovarian tissue. Supplementation has been associated with reduced fasting insulin, improved ovulatory function, regularized menstrual cycles, lower testosterone levels, and increased sex SHBG, making them beneficial for both reproductive and metabolic symptoms of PCOS [23, 42, 43].

Folic acid (Vitamin B9), essential for methylation and DNA synthesis, has been shown to reduce elevated homocysteine levels, a known cardiovascular risk factor in PCOS. Additionally, it may support glycemic control and reduce oxidative stress, particularly in overweight or obese women [44].

Omega-3 fatty acids, particularly EPA and DHA, pose anti-inflammatory and insulin-sensitizing properties, contributing to improved lipid profiles, reduced triglycerides, and enhanced insulin sensitivity. However, their impact on weight loss and androgen levels appears limited, suggesting their primary role in metabolic management rather than reproductive outcomes [45].

Probiotics have emerged as a promising complementary therapy due to their ability to improve gut microbiota diversity, often reduced in women with PCOS. Supplementation has been associated with improved insulin sensitivity, reduced inflammation, and lower oxidative stress markers, although long-term effects on hormonal balance and metabolic outcomes remain to be fully established. Additional supplements such as alpha-lipoic acid, selenium, zinc,

magnesium, and coenzyme Q10 have shown promise in improving glycemic control, reducing oxidative stress, enhancing mitochondrial function, and lowering androgen levels. While these findings are encouraging, large-scale randomized controlled trials are necessary to confirm their long-term safety and efficacy in PCOS management [39, 46, 47].

*Alternative Medicine for PCOS*

*Cinnamomum verum* (cinnamon), especially when combined with *Glycyrrhiza spp.* and *Paeonia lactiflora*, has been associated with reductions in BMI, insulin levels, and cholesterol. However, its effects on fasting glucose and testosterone appear minimal. *Lagerstroemia speciosa* and *Cinnamomum burmannii* have demonstrated significant BMI reduction over six months. *Terminalia chebula* (Haritaki) improves glucose and lipid metabolism, possesses antioxidant and anti-inflammatory properties, and may aid in insulin resistance (IR) prevention. Other herbs like *Trigonella foenum-graecum* (Fenugreek), *Vitex agnus-castus* (Chasteberry), and *Cimicifuga racemosa* (Black Cohosh) may contribute to menstrual regularity and fertility enhancement. *Nigella sativa* (Black Cumin) has shown positive effects on ovarian function and IR in animal models. *Cimicifuga racemosa,* when combined with clomiphene, may improve fertility outcomes. Berberine, either alone or in combination with metformin, has been shown to enhance glucose metabolism. While data on anti-androgenic effects remain limited, herbs like *Anethum graveolens* (Dill) and *Matricaria chamomilla* (Chamomile) have been suggested to reduce testosterone and alleviate hirsutism symptoms [2, 48, 49].

Acupuncture also emerged asa potential adjunct therapy for PCOS management. Vagus nerve stimulation (VNS), a form of acupuncture, may help modulate inflammation by inhibiting pro-inflammatory cytokines. VNS has demonstrated therapeutic effects in conditions such as diabetes, epilepsy, and autoimmune disorders by influencing the hypothalamic-pituitary-adrenal axis, thereby enhancing cortisol release and insulin metabolism. A non-invasive variant, transcutaneous auricular vagus nerve stimulation (taVNS), specifically targets the ear and has shown benefits in improving mood and cognitive function, particularly in treatment-resistant depression, which is commonly observed in PCOS patients. While taVNS has been linked to enhanced emotional well-being and alertness, its direct impact on PCOS symptoms requires further clinical investigation [2, 50].

## Conclusion

Polycystic ovary syndrome requires a personalized, multidisciplinary treatment approach due its complex metabolic, reproductive, and psychological manifestations. Lifestyle modifications, including weight management and increased physical activity, remain first-line interventions, offering substantial improvements in insulin sensitivity and hormonal balance. Pharmacological therapies, such as hormonal contraceptives, metformin, and antiandrogens, play a pivotal role, particularly when lifestyle changes alone prove insufficient. Emerging medications, including glucagon-like peptide-1 receptor agonists, offer promising metabolic benefits, especially in obese women with polycystic ovary syndrome.

Complementary therapies, including herbal medicine and acupuncture, are gaining recognition as adjunct treatments. Herbal agents like Cinnamomum verum, Nigella sativa, and Terminalia chebula show potential metabolic and reproductive benefits, while acupuncture and vagus nerve stimulation may aid in inflammation regulation and mood stabilization. Despite these advances, further high-quality research is required to establish the long-term efficacy and safety of alternative treatments in polycystic ovary syndrome.

Mowing forward, an individualized treatment plan incorporating lifestyle changes, pharmacotherapy, and complementary therapies remains the most effective strategy for managing the complex symptoms of polycystic ovary syndrome. Continued research and evidence-based guidelines will be essential to refining therapeutic approaches and improving patient outcomes.

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# HYPERSENSITIVE REACTIONS TO CHEMOTHERAPY

# *HIPERSENZITIVNE REAKCIJE NA HEMIOTERAPIJU*

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**Abstract**

**Introduction.** Despite advancements in therapeutic modalities, chemotherapy remains the cornerstone of treatment for a wide range of malignancies. However, all chemotherapeutic agents have the potential to induce hypersensitivity reactions. **Literature Review.** Platinum-based compounds and taxanes are the most frequently implicated in hypersensitivity reactions. The most commonly used classification systems for these reactions are the Brown classification and the Common Terminology Criteria for Adverse Events. Diagnostic approaches include *in vivo* provocation tests and in vitro assays. Optimal results from skin tests are achieved when performed between six weeks and six months after an allergic reaction. A positive skin test indicates a significant risk of anaphylaxis upon drug re-administration without precautionary measures. If no suitable alternative therapy is available, desensitization should be undertaken before reintroducing the drug. The process involves the controlled, stepwise administration of the drug, starting with a low dose and gradually increasing it under strictly monitored conditions. **Conclusion.** A thorough understanding the molecular mechanisms underlying hypersensitivity reactions, along with familiarity with their clinical presentation, classification, and diagnostic strategies, is essential for identifying suitable candidates for desensitization. Additionally, the involvement of a multidisciplinary team comprising allergists and oncologists is crucial in evaluating oncology patients and determining the most appropriate therapeutic approach for each individual case.

**Key words:** Antineoplastic Agents; Drug Therapy; Hypersensitivity; Desensitization, Immunologic; Skin Tests

**Sažetak**

**Uvod.** Uprkos novim terapijskim modalitetima, hemioterapija i dalje predstavlja okosnicu lečenja širokog spektra zloćudnih bolesti, a svi hemioterapijski agensi mogu izazvati reakcije preosetljivosti. **Pregled literature.** Najveći broj hipersenzitivnih reakcija uzrokuju jedinjenja platine i taksani. Najčešće korišćene klasifikacije hipersenzitivnih reakcija su Braunova klasifikacija i Zajednički terminološki kriterijumi za neželjena dejstva. Dijagnostički testovi se dele na *in vivo* provokacione testove i in vitro testove. Najbolje rezultate dobijamo ukoliko kožne testove sprovodimo u periodu od šest nedelja do najkasnije šest meseci od alergijske reakcije. Pozitivni rezultati kožnih testova pokazuju da je pacijent pod značajnim rizikom od anafilaksije ako se lek ponovo primeni bez mera opreza. Pre ponovne primene leka potrebno je sprovesti desenzibilizaciju ukoliko ne postoji ekvivalentna supstituciona terapija. Desenzibilizacija uključuje ponovnu primenu leka u visokokontrolisanim uslovima, koristeći postupne korake u kojima se najpre primenjuje niska doza leka, a kroz svaki sledeći korak doza se postepeno povećava. **Zaključak**. Razumevanje molekularnih mehanizama hipersenzitivnih reakcija, poznavanje njihove kliničke slike i klasifikacije, kao i poznavanje dijagnostičkih testova ključni su za pravilan odabir bolesnika za desenzibilizaciju. Važno je naglasiti važnost multidisciplinarnog tima alergologa i onkologa u evaluaciji onkoloških bolesnika i donošenju odluka za primenu najboljeg terapijskog modaliteta za svakog pojedinog bolesnika.

**Ključne reči:** hemioterapijski agensi; hemioterapija; hipersenzitivna reakcija; imunološka desenzitizacija; kožni testovi

## Introduction

For nearly nine decades, chemotherapy has played a pivotal role in the treatment of malignant diseases. Despite advancements in therapeutic modalities, it remains the cornerstone of cancer treatment [1, 2]. However, all chemotherapeutic agents have the potential to induce hypersensitivity reactions (HCR), which are the third leading cause of fatal drug-induced anaphylaxis in the United States [2]. Therefore, whenever feasible, chemotherapy should be limited in favor of targeted therapies [3]. Platinum-based compounds and taxanes account for the majority of HCR cases, which may be mediated by IgE-dependent or non-IgE mechanisms and present with varying clinical manifestations. Prompt recognition and management of life-threatening hypersensitivity reactions are crucial. Identifying high-risk patients allows for proper risk assessment and informed decision-making regarding further treatment [4]. Desensitization is a safe and highly effective strategy, with breakthrough reactions occurring infrequently and typically presenting as mild [5].

## Literature review

### *Platinum derivatives*

Among chemotherapeutic agents, platinum derivatives are the most common triggers of HCR [2].

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***Abbreviations***

HCR – hypersensitive reactions
IgE – immunoglobulin E
BRCA 1/2 – breast cancer gene
IL-6 – interleukin six
TNF-α – tumor necrosis factor alpha
SCAR – Severe Cutaneous Adverse Reactions
SJS/TEN – Stevens-Johnson syndrome/toxic epidermal necrolysis
CT – computed tomography
IL-1ß – interleukin one beta
CTCAE – Common Terminology Criteria for Adverse Events
ACE – angiotensin converting enzyme

The primary platinum-based drugs include cisplatin, oxaliplatin, and carboplatin, while nedaplatin, heptaplatin, and lobaplatin are available only in Asia [1] **(Table 1)**.

Published data indicate that over 20% of patients receiving platinum-based chemotherapy experienced allergic reactions [6]. The most significant risk factor for HCR to platinum agents is prior exposure, with incidence rates increasing from 1% after the first six cycles to 27% beyond the seventh cycle of carboplatin. The peak occurrence is observed around the eighth or ninth cycle [8], with similar patterns reported for cisplatin and oxaliplatin [7]. Additionally, increased HCR rates have been noted in women with BRCA 1/2 mutations [1, 2, 9]. In pediatric patients receiving carboplatin for brain tumors, the incidence of HCR has been reported at 42% [10].

Cross-reactivity between carboplatin and oxaliplatin is estimated at 37-45%, whereas patients who experience HCR to either drug have a significantly lower risk when switched to cisplatin due to it minimal cross-reactivity [10]. Nedaplatin has been explored as an alternative for patients with carboplatin-induced HCR. A recent study confirmed its favorable safety profile, with only one reported case of HCR [1].

The majority of platinum-induced HCR are IgE-mediated type I hypersensitivity reactions, initially described in refinery workers exposed to platinum salts. This was later confirmed by the detection of carboplatin-specific IgE antibodies [11]. Immediate

**Table 1.** Characteristics of immediate hypersensitive reactions on platinum derivatives

| Chemotherapeutic agent | Malignancies in which it is used | Time to HCR onset | Characteristics of HCR |
|---|---|---|---|
| Carboplatin | • Ovarian cancer<br>• Lung cancer<br>• Squamous cell carcinoma of head and neck | Maximum rate of HCR occurs when applying the 8th or 9th cycle<br>• 1% between 1-6th cycle<br>• 27% when applying for the 7th cycle or subsequent ones | Redness, itching, urticaria Approximately 50% of HCRs are moderately severe with diffuse erythroderma, wheezing, facial swelling, nausea/vomiting, diarrhea, dyspnea, hypotension, or anaphylaxis |
| Cisplatin | • Gynecological malignancies<br>• Lung cancer<br>• Squamous cell carcinoma of head and neck | Increases with the number of cycles and simultaneous irradiation; higher rate after the 6th cycle | Urticaria, itching, respiratory distress, hypotension |
| Oxaliplatin | Gastrointestinal malignancies, especially colon cancer in combination with leucovorin and fluorouracil (FOLFOX) | Increases with the number of cycles; up to 20% after the 6th cycle | Flushing, pruritis, urticaria, palmar erythema, angioedema, hypertension, hypotension, dyspnea, chest tightness, cough, throat tightness, nausea, diarrhea. Less often - temperature, chills, shivering, stiffness, back pain. Neurological (tingling, dizziness). Rarely, thrombocytopenia, hemolytic anemia, and bleeding. |
| Albumin bind paclitaxel<br>Cremofor bind Paclitaxel<br>Docetaxel | • Breast cancer<br>• Ovarian cancer<br>• Non-small cell lung cancer<br>• Squamous cell cancer of head and neck<br>• Kaposi sarcoma (paclitaxel)<br>• prostate cancer (docetaxel)<br>• Stomach adenocarcinoma (docetaxel)<br>• Adenocarcinoma of pancreas (paclitaxel) | At first exposure during the 1st or 2nd cycle | Flushing, chest pain, back pain, abdominal pain, respiratory symptoms (dyspnea, chest tightness, wheezing, throat tightness), gastrointestinal symptoms (nausea, vomiting, diarrhea), hypertension, hypotension, fluid retention. |
| Cabizataxel | Second line metastatic, hormone resistant, prostate cancer | | |

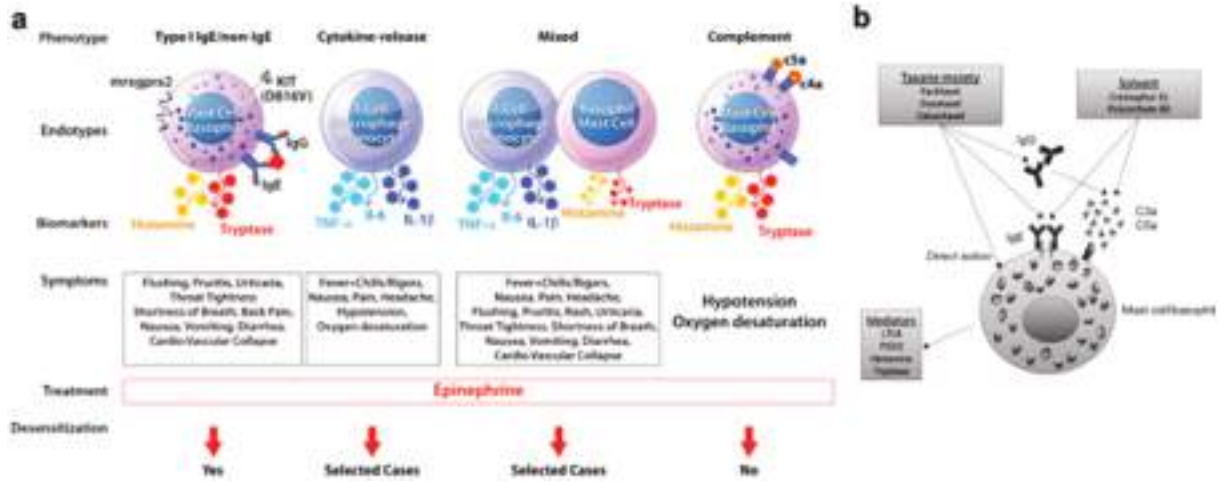


**Figure 1.** Mechanisms of immediate hypersensitive reactions on platinum and taxanes. Available at: https://doi.org/10.1007/s12016-021-0887

reactions commonly present as pruritus of the palms and soles, erythema and urticaria. However, platinum agents have also been associated with several cases of type II hypersensitivity reactions, such as immune-mediated hemolytic anemia and thrombocytopenia (with oxaliplatin), sometimes complicated by bleeding, and type III hypersensitivity reactions, including delayed urticaria as part of vasculitis.

Skin testing and desensitization play no role in type II and type III hypersensitivity reactions, but the drug should be permanently discontinued [10].

A new classification of HCR integrates phenotypes, endotypes and biomarkers. Phenotypes of platinum-induced HCR **(Figure 1)** include immediate and delayed reactions, categorized into type I hypersensitivity reactions, cytokine release reactions, and mixed reactions, with the greatest heterogeneity observed with oxaliplatin [7]. Endotypes define the underlying immunological mechanisms, while biomarkers facilitate their identification [6]. Oxaliplatin-induced HCR are particularly heterogeneous, often presenting as cytokine release reactions characterized by fever, chills, rigors, headache, chest pain, or back pain, accompanied by elevated IL-6 and TNF-α levels [12].

*Taxanes*

Taxanes are complex alkaloid esters used in the treatment of various malignancies including breast, prostate, head and neck, lung, and gynecological cancers. The main taxanes include paclitaxel, docetaxel, nab-paclitaxel, and cabazitaxel. Paclitaxel was originally derived from the Pacific yew tree, while docetaxel is produced via a semisynthetic process [13]. Although structurally similar, taxanes differ in their solvents>: paclitaxel is formulated with Cremofor EL, whereas docetaxel and cabazitaxel use polysorbate 80 [2]. Cremofor EL has been shown to induce direct complement activation, leading to the release of anaphylatoxin and subsequent mast cell and basophil activation. In patients with prior anaphylactic reactions to docetaxel and paclitaxel, the use of nanoparticles bound to albumin (nab-paclitaxel), which lacks Cremofor EL, has been associated with a lower incidence of HCR [2]. However, severe immediate HCR have still been reported with nab-paclitaxel [7].

Taxanes are highly allergenic, with early studies reporting immediate HCR rates as high as 50% for paclitaxel and docetaxel, prompting the routine use of antihistamines and corticosteroids for premedication [13]. Most HCR occur within minutes, typically during the first or second exposure to the drug [7]. Cross-reactivity between paclitaxel and docetaxel has been reported in two studies, and an association between taxanes and tryptase allergens has been demonstrated [14]. One example of IgE-mediated HCR involves individuals previously exposed to yew pollen, who may develop hypersensitivity to taxanes [13]. Additionally, paclitaxel has been isolated from hazelnuts, and cases of cross-reactivity between paclitaxel and hazelnut consumption have been documented [15, 16].

Immediate HCR to paclitaxel and docetaxel occur in approximately 10% of patients, with severe reactions reported in 1% of cases despite premedication [7, 8, 17]. Symptoms typically manifest 15 minutes after infusion onset and include dyspnea (with or without bronchospasm), urticaria, hypotension (or hypertension), delayed erythematous rash (which may begin hours or weeks after drug application), and severe pain in the back, pelvis, chest, and abdomen [7, 8, 18]. Unlike platinum agents, 90% of taxane-induced HCR occur within the first two treatment cycles [1]. This pattern suggests a mechanism involving direct process

of mast cell degranulation. A case report described a fatal anaphylactic reaction to paclitaxel, where the patient experienced lip swelling and urticaria ten days after chemotherapy administration [19].

In 10-15% of cases, HCR to taxanes present as delayed skin reactions, emerging – several days up to 10 days post-administration of docetaxel. These reactions range from mild maculopapular exanthema, urticaria, and angioedema to severe cutaneous adverse reactions (SCAR) and may also involve other organs such as the lungs, liver, and kidneys [6]. Most of the mild reactions resolve within a few days with symptomatic treatment [10]. However, severe delayed reactions to paclitaxel include interstitial pneumonitis, which is associated with for a high risk of mechanical ventilation and mortality [20]. Severe reactions such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute interstitial pneumonitis, and subacute cutaneous lupus erythematosus have been documented with paclitaxel, docetaxel, and nab-paclitaxel [8, 13].

Interstitial pneumonitis may develop days to weeks after docetaxel and paclitaxel administration, occurring less frequently with nab-paclitaxel and docetaxel. Clinical manifestations include exertional dyspnea, dry cough, fatigue, and low-grade fever. High-resolution CT (HRCT) typically reveals ground-glass opacities, which may be diffuse or present as centrilobular nodules, corresponding to non-fibrotic hypersensitivity pneumonitis. In contrast, fibrotic hypersensitivity pneumonitis is characterized by traction bronchiectasis, bronchioloectasis, honeycombing, and bronchiolitis, with HRCT findings displaying the "headcheese" or "triple density" sign [21]. Management is primarily supportive, with taxane discontinuation at the first step. The initiation of glucocorticoid therapy depends on the severity and progression of lung involvement [22].

Another notable adverse effect is capillary leak syndrome, observed with docetaxel. It is characterized by peripheral edema, dyspnea, non-cardiogenic pulmonary edema, and pleural effusions, with weight gain often being the earliest sign. Prompt diuretic therapy at symptom onset may help prevent severe fluid retention complications [22].

Immediate HCR typically occur within 1-6 hours post-administration, and this phenotype is most often associated with either IgE-mediated endotype or the endotype of direct complement activation. Delayed type IV hypersensitivity reactions, which appear days to weeks after drug exposure, most commonly manifest as maculopapular exanthema or severe SCAR [6]. Solvent taxanes such as Cremofor EL (paclitaxel) and polysorbate 80 (docetaxel) can activate mast cells either via an IgE-mediated mechanism or through direct complement activation, leading to C3a and C5a anaphylatoxin release **(Figure 2)**. Additionally, histamine release has been observed during the direct action of paclitaxel on basophils [13]. Biomarkers include: tryptase, histamine, leukotrienes and prostaglandins in type I reactions, and IL-6, TNF-α and IL-1ß

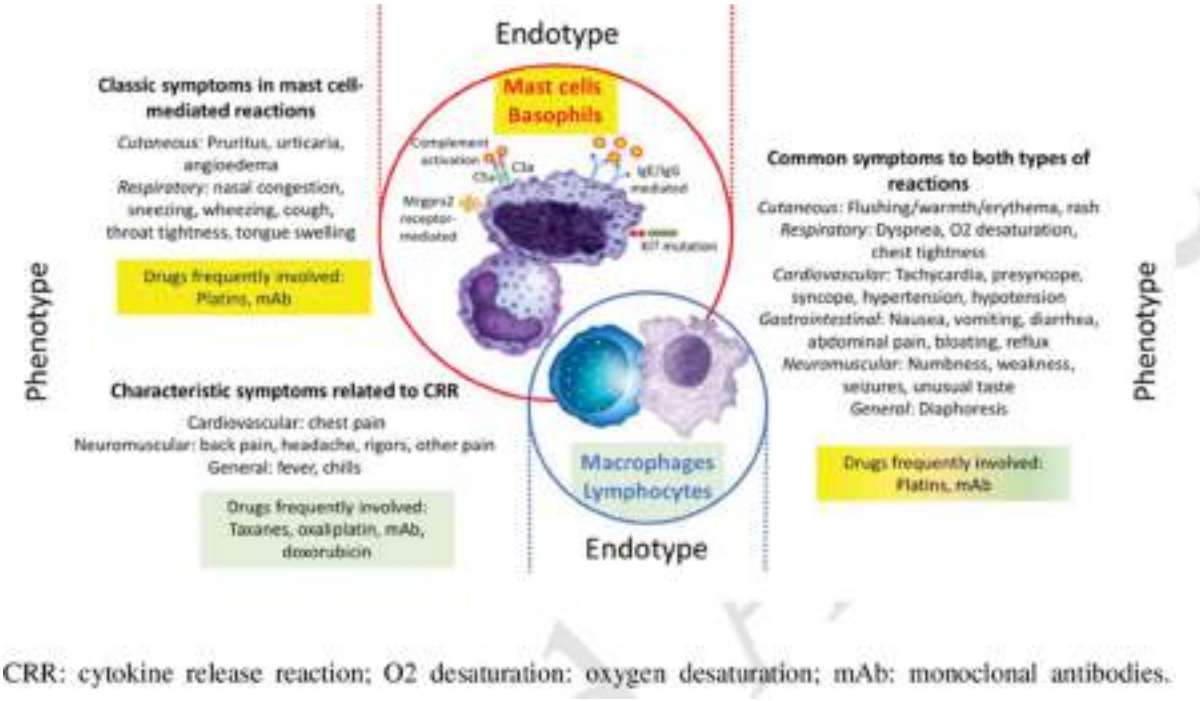


**Figure 2.** Phenotypes and endotypes of hypersensitive reactions to chemotherapy and monoclonal antibodies. Available at: https://pubmed.ncbi.nlm.nih.gov/34045179/

in cytokine release or mixed reactions [1, 7]. Desensitization is indicated for type I reactions and selected cases of cytokine release or mixed reactions. However, it is not effective for reactions caused by direct mast cell or basophil activation [7].

*Classification of HCR*

Classifying hypersensitivity reaction is essential for assessing severity and guiding therapeutic decisions. The most widely used classifications are the Brown classification and the Common Terminology Criteria for Adverse Events (CTCAE) [7].

*Diagnosis*

Classifying hypersensitivity reaction diagnosis is based on clinical history, physical examination, symptomatology, and diagnostic tests. These tests are categorized into in vivo provocation tests and in vitro tests. In vivo provocation tests include skin (prick and intradermal) and dose provocation tests. Skin tests are sensitive, widely used, cost-effective, and rapid methods for detecting IgE-mediated allergic reactions. Their main advantages over in vitro tests are their immediacy (results within 15 to 20 minutes), and patient involvement, enhancing understanding of allergic responses [23]. The most extensively studied agents for skin testing are platinum derivatives and taxanes [1]. Other antineoplastic agents can also be tested, provided that they do not induce skin necrosis upon extravasation. Irritant drugs must be diluted appropriately to prevent non-allergic skin irritation. Testing begins with a prick test, followed by an intradermal test if the prick test is negative [10]. Intradermal testing involves injecting a small drug dose into the dermis, increasing sensitivity due to enhanced exposure of cutaneous mast cells [1]. However, several systemic reactions have been reported during intradermal testing [23]. These reactions result from histamine release, leading to smooth muscle contraction and increased vascular permeability. At the same time, inflammatory mediators activate neuron reflex mechanisms, with secondary vasodilatation and erythema [1].

Patients with a history of severe HCR to platinum derivatives should undergo skin testing before re-exposure. If positive, desensitization is necessary [10]. Carboplatin and oxaliplatin skin tests are particularly valuable for predicting HCR risk during desensitization, as positive test results correlate with an increased likelihood of recurrent reactions [2]. Intradermal testing is necessary with carboplatin as 86.4% of positive skin tests are confirmed through this method [7, 11]. The concentrations used for testing affect the predictive value of skin tests. Lower concentrations (1-5 mg/mL) yield 41-75% positivity, while 10 mg/ml increased detection rates to 81-88% [7].

Optimal testing occurs 6 weeks to 6 months after HCR; delays beyond six months increase false-negative results. The time period between the performance of the skin test and prior exposure to carboplatin or HCR is important for test result interpretation. Testing is recommended at least 4-6 weeks after the initial HCR, although some studies suggest a 2–week window [11, 22]. However, false negative results may occur. In one study, 5 of 37 (13.5%) patients tested negative within 10 days of immediate HCR but later converted to positive on repeat testing [24].

Positive skin test results indicate high anaphylaxis risk if the drug is re-administered without precautions. Desensitization is required before re-administration of the drug if no alternative therapy exists [10]. Negative skin test results allow for drug re-administered under lower-concentration protocols, gradual dose increase, and additional premedication [10].

If previous standard tests are negative or unavailable, and after a careful risk–benefit assessment, a dose challenge test may be performed – the gold standard for diagnosing HCR [1]. Dose challenge test with platinum derivatives involves administering 1/10 of the full dose at the normal infusion rate without premedication, observing for 30 minutes for any reaction, and if no symptoms appear, administering the remaining 9/10 of the dose. If no symptoms appear, the absence of allergy is concluded and future drug use is allowed [10]. Contraindications for dose challenge test include uncontrolled asthma, pregnancy, beta-blocker use, cardiac disease history, vasculitis, bullous exanthemas, acute generalized exanthematous pustulosis, and severe anaphylaxis history [1].

In vitro tests include determination of specific IgE (sIgE), total IgE (tIgE), basophil activation test (BAT), and tryptase measurement [1]. Mast cells and basophils contain various chemical mediators that are released into the circulation during anaphylaxis. Serum tryptase concentration peaks 3 hours post reaction. Testing within 1-3 hours of symptom onset is recommended as earlier samples (< 30 minutes) may yield false negatives [10]. The lymphocyte transformation test in vitro assesses T-cell proliferation in response to an antineoplastic drug but is technically demanding clinically. The specific IgE test for oxaliplatin was validated in 2015 through a prospective study. For platinum derivatives, specific IgE testing is important for diagnosis (recommendation level B) [2]. Skin testing and measuring the level of chemical mediators are crucial for evaluating HCT during desensitization [10].

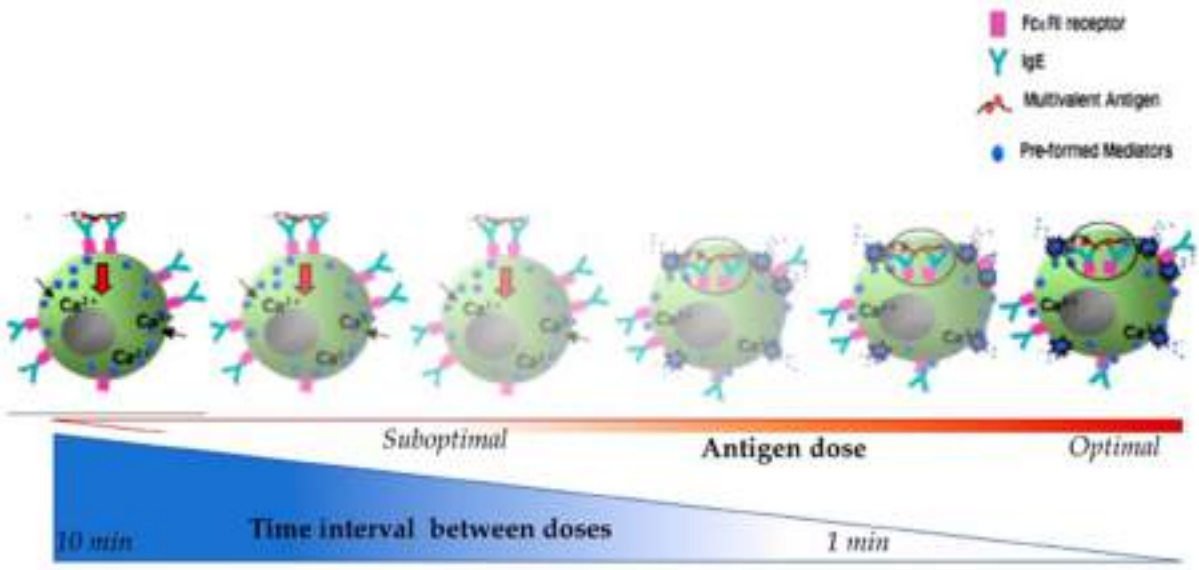


**Figure 3.** Schematic diagram showing mast cell β-hexosaminidase in relation to time interval between antigen administration and antigen dose during desensitization. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC5486137/

*Desensitization*

The origins of desensitization trace back to the 1980s when the first intravenous and oral penicillin desensitization protocols were established [6]. Desensitization involves the controlled re-administration of a drug in gradually increasing doses, starting with a low initial. The process must be repeated each time the drug administered [10]. The time intervals and dosage increments during desensitization are crucial. If suboptimal doses are administered every minute, mediator inhibition is reduced, whereas ten-minute intervals maximize inhibition **(Figure 3).** Additionally, suboptimal doses cause less mediator release than optimal doses. Shorter intervals or excessively high suboptimal dose can increase β-hexosaminidase release, leading to breakthrough reactions (when the drug is applied too quickly) [6]. Desensitization is contraindicated in cases of exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and immune thrombocytopenia caused by chemotherapy [2]. Patients are stratified into high- and low-risk groups based on specific risk factors. The high-risk group includes pregnant women, patients with positive skin tests or Grade III HCR, and those on beta-blockers or ACE inhibitors. It also includes individuals with comorbidities such as cystic fibrosis, mastocytosis, coronary disease, or hypertension [2].

Desensitization must be conducted by an allergist or in an intensive care unit to allow for immediate anaphylaxis management. Rapid desensitization protocols are not recommended for patients with IgE-mediated anaphylactic reactions, particularly those related to platinum derivatives. During desensitization, mild symptoms commonly occur, especially in the later stages of drug administration [10]. Mast cell unreactivity has been attributed to impaired FcεR1 receptor internalization due to progressive cross-linking at low antigen concentration, indicating that the receptors are exhausted before the next dose. Unlike in activated cells, where antigen/IgE/FcεR1 complexes are internalized, these complexes remain on the surface during desensitization [6].

According to Leticia de las Vecillas Sanchez and colleagues, rapid desensitization inhibits mast cell activation in all fields by impairing antigen/IgE/FcεR1 complex internalization, preventing calcium flux, and releasing lipid mediators, and cytokine production [6].

## Conclusion

A comprehensive understanding of the molecular mechanisms of hypersensitive reactions, their clinical presentation, classification, and diagnostic methods is essential for selecting appropriate candidates for desensitization. Risk assessment and prompt intervention in case of severe anaphylactic reactions are crucial. A multidisciplinary team of allergists and oncologists plays a pivotal role in evaluating oncology patients and determining the most suitable therapeutic approach for each individual case.

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PROFFESIONAL ARTICLES
*STRUČNI ČLANCI*

# VARIABLES, DATA, AND DESCRIPTIVE STATISTICAL METHODS – PART I

## *VARIJABLE, PODACI I DESKRIPTIVNE STATISTIČKE METODE – DEO I*

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**Abstract**

**Introduction**. Statistics play a crucial role in clinical practice, enabling the comprehension of professional and scientific literature. A fundamental understanding of variables, data, and both descriptive and inferential statistics is essential. **Variables.** Variables represent characteristics that differ between subjects. They are measured, and their values are expressed by data. **Scales of measurement**. There are four measurement scales: nominal, ordinal, interval, and ratio. The nominal scale classifies qualitative variable into distinct categories without any inherent order. The ordinal scale categorizes qualitative variables in a specific sequence, though the differences between categories lack a defined numerical meaning. The interval scale applies to quantitative variables, ensuring that the differences between successive values are equal, but it lacks an absolute zero. The ratio scale also features equal intervals between values but includes an absolute zero, allowing for meaningful ratio comparisons. **Descriptive statistics**. Descriptive statistics summarize and numerically represent data to enhance clarity and interpretability. This includes measures of frequency, central tendency, variability, and distribution shape, alongside tabular and graphical data presentations. **Conclusion**. This article outlines fundamental concepts related to variables, data, and descriptive statistics, providing practical examples to illustrate their application.

**Key words**: Statistics as Topic; Data Collection; Normal Distribution; Clinical Medicine

**Sažetak**

**Uvod.** Statistika je neophodna u kliničkoj praksi zbog praćenja stručne i naučne literature. Stoga, treba poznavati osnovne koncepte povezane sa varijablama, podacima, deskriptivnom te inferencijalnom statistikom. **Varijable.** Varijable su obeležja koja se mogu menjati od jednog ispitanika do drugog. Mere se i njihove vrednosti se izražavaju podacima. **Skale merenja.** Postoje četiri skale merenja: nominalna, ordinalna, intervalna i skala odnosa. Nominalna skala samo rangira kvalitativnu varijablu u kategorije bez bilo kakvog redosleda. Ordinalna skala rangira kvalitativnu varijablu u kategorije po određenom redosledu, pri čemu rastojanja između kategorija nemaju precizno značenje. Intervalna skala podrazumeva da su rastojanja između uzastopnih vrednosti kvantitativne varijable uvek jednaka, ali da ne postoji apsolutna nulta tačka. Skala odnosa, pored jednakosti rastojanja između uzastopnih vrednosti kvantitativne varijable, ima i apsolutnu nulu. **Deskriptivna statistika.** Deskriptivna statistika je oblast statistike koja se bavi sumiranjem i numeričkim opisivanjem podataka kako bi bili jasni i razumljivi. Numeričko opisivanje podataka se očituje u merama učestalosti, merama centralne tendencije, merama varijabilnosti, merama oblika raspodele te tabelarnom i grafičkom predstavljanju podataka. **Zaključak.** Ovaj stručni rad, kroz primere, opisuje osnovne koncepte koji se odnose na varijable, podatke i deskriptivnu statistiku.

**Ključne reči**: statistika; prikupljanje podataka; normalna distribucija; klinička medicina

### Introduction

Statistics are an essential component of clinical research [1, 2]. But why is this the case? Why it is statistical analysis indispensable? Clinicians work with biological systems that are inherently variable. For instance, when healthy individuals are exposed to a virus such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), their response can vary significantly – from no infection to asymptomatic, mild or moderate infection, to severe disease with potentially fatal outcomes [3, 4]. Consider a scenario where an individual receives a vaccine prior to viral exposure and does not develop an infection. Given the natural variability in immune responses, it would be difficult to conclude that the vaccine was protective based on a single case. To address this, clinical studies compare two groups: one receiving the vaccine and the other not. By monitoring infection rates in both groups and applying statistical analysis, researchers can determine whether observed differences are due to chance or a true effect of the intervention.

Beyond research, statistical literacy is crucial for clinicians to understand and critically evaluate sci-

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***Abbreviations***

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus-2
COVID-19 – Corona Virus Disease of 2019

entific literature [1]. Medical knowledge is rapidly evolving, with new diagnostic techniques, therapies, and even emerging – such as COVID-19 – continually reshaping clinical practice. Relying solely on textbook knowledge, while disregarding the latest clinical evidence, is professionally unacceptable. A lack of statistical understanding may hinder clinicians from correctly interpreting study findings, potentially preventing patients from receiving the most effective and safest treatment. Therefore, familiarity with fundamental statistical concepts – including variables, data types, descriptive and inferential statistics is essential [5].

However, research indicates that many clinicians have a limited grasp of basic statistical principles [6-8]. For example, a study by Alomi et al. found that pharmacists scored an average of 64.6% on statistical knowledge test [6]. Similarly, Collins et al. highlighted a lack of statistical proficiency among surgeons and emphasized the importance of continuing education [7]. In another study, Jahan et al. reported that 73.6% of primary care physicians rated their statistical knowledge at or below 5 on a 10-point scale and expressed interested in improving it [8].

This article provides an overview of fundamental concepts related to variables, data, and descriptive statistics.

## Variables

Variables are characteristics that vary between subjects, with their values represented as data. For example, sex is a variable, while is the classification of an individual as male or female constitutes data. Before conducting a clinical study, it is essential to consider the nature and type of variables, as they influence how data is described and analyzed.

The two primary types of variables are qualitative and quantitative, as illustrated in **Figure 1** [9, 10].

Qualitative variables categorize characteristics into distinct groups and are often referred to as categorical variables. Their measurement provides information about the frequency of characteristics within a group. These variables can be nominal or ordinal **(Figure 1).** Nominal variables classify data into categories without an inherent order, such as sex (male or female), marital status (single, married, or divorced), or presence of osteoporosis (yes or no). Ordinal variables have categories arranged in a meaningful order. Examples include educational level (elementary, high school, or college), pain intensity (rated on a 0-10 scale), and symptom frequency (never, rarely, sometimes, often, or always).

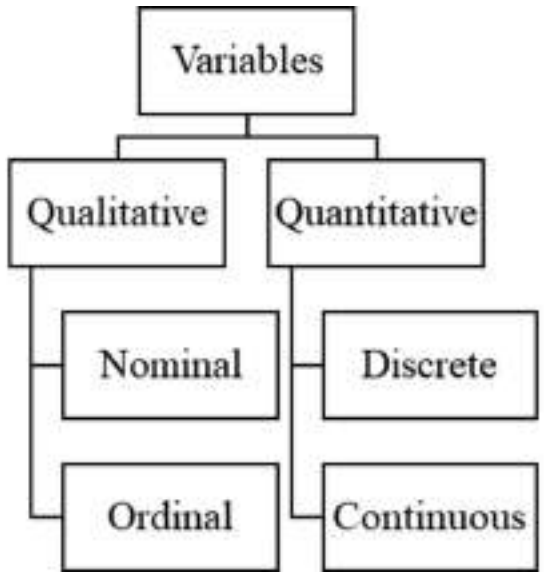


**Figure 1.** Types of variables

Quantitative variables are measured using a device or standardized evaluation method and are often termed numerical variables. They provide information about the quantity of a characteristic and can be classified as discrete or continuous **(Figure 1).** Discrete variables assume specific numerical values, typically integers. Examples include age, number of students in a classroom, and number of hospitalizations. Continuous variables can theoretically take any value within a given range. However, measurement precision is limited by the accuracy of the instrument. For instance, a patient's actual blood glucose level might be 5.2372 mmol/L, but a device may only record it as 5.2 mmol/L. Examples of continuous variables include body mass and height and blood glucose concentration.

In addition to their classification as qualitative or quantitative, variables are also categorized as dependent or independent based on their role in a study [10]. The dependent variable is the outcome being studied – it is a characteristic that researchers aim to explain or predict. The independent variable is the factor manipulated or observed to determine its effect on the dependent variable. For example, in a study examining the relationship between sex and cardiovascular morbidity, the dependent variable is cardiovascular morbidity, while the independent variable is sex. Typically, studies have a small number of dependent variables (one or, in some cases, a few), whereas the number of independent variables can be extensive.

**Scales of measurement**

There are four primary scales of measurement: nominal, ordinal, interval, and ratio [9, 10].

Nominal scale measurements classify qualitative characteristics into distinct categories without any inherent order. These categories are entirely different from one another, and any numerical or alphabetical coding assigned to them serves only as a label rather than representing actual quantities (e.g., 1 – female, 2 – male). A nominal scale with only two categories is referred to as a dichotomous or binary scale.

Ordinal scale measurements categorize qualitative characteristics in a ranked order, but the differences between categories do not have a precise numerical meaning. For example, pain intensity rated on a 0-10 scale follows an ordinal structure (category 2 < category 4 < category 8), but the difference between 4 and 8 does not imply that pain is twice as intense as category 4.

Interval scale measurements ensure that the difference between successive values is always equal, but they lack an absolute zero point, only an arbitrary one. A classic example is temperature measured in degrees Celsius, where the difference between 10°C and 20°C is the same as that between 30°C and 40°C; however, 40°C is not twice as hot as 20°C, as zero degrees does not represent the complete absence of heat.

Ratio scale measurements have an equal distance between successive values but also include an absolute zero, making meaningful ratio comparisons possible. For example, temperature in Kelvin is measured on a ratio scale, where 0 Kelvin represents the absence of molecular motion [10].

Categorical variables are measured using nominal or ordinal scales, whereas continuous variables are measured on an interval or ratio scales [10].

**Descriptive statistics**

Descriptive statistics summarize and numerically represent data, making statistical summarization essential for meaningful analysis.

Numerical data description is categorized into several groups: measures of frequency, measures of central tendency, measures of variability, measures of distribution shape, and tabular and graphical data presentation [9].

*Measures of frequency*

Measures of frequency indicate how often a value appears within a dataset. These include count, percentage and frequency, which are primarily used for categorical data measured on nominal and ordinal scales. For example, Nikolić et al. presented in Tables 2-5 in their article drug interactions data in terms of frequency and percentage [11].

*Measures of central tendency*

Measures of central tendency describe how data cluster around a central value, providing a representative metric for comparison across groups. The three most commonly used measures are the mean, median, and mode [12, 13].

The mean (arithmetic mean) is an appropriate measure for data measured on an interval or ratio scale with a normal distribution. It is calculated by dividing the sum of all values by the total number of observations. However, it is highly sensitive to outliers, i.e. data with extremely low or extremely high values.

The median is the middle value when data are arranged in ascending order. It is suitable for ordinal data, datasets with outliers, and continuous data that do not follow a normal distribution. It is the value that divides the series, where data is sorted by size, into two equal parts. There is an equal number of data (50%) above and below the median. If there is an odd number of observations, the median is the middle value. If there is an even number, it is the average of two central values.

The mode represents the most frequently occurring value in a dataset and is primarily used for nominal data. A variable may have one mode, two modes, multiple modes, or no mode at all.

*Measures of variability*

While measures of central tendency summarize data with a single representative value, they do not provide insight into how individual data points deviate from the mean or from each other. This variability, also referred to as dispersion, is crucial for understanding the distribution of data. Several statistical measures quantify variability, the most common being range, interquartile range, variance, and standard deviations [12, 13]. Broadly, range and interquartile range assess the spread of data points relative to each other, while variance and standard deviation measure how data points deviate from the mean.

Range is a measure of variability applicable to ordinal, interval, and ratio scale. It is calculated as the difference between the maximum and minimum values. However, due to its sensitivity to extreme values (outliers), the range is generally unsuitable for clinical studies, where outliers frequently occur.

Interquartile range is a measure of variability used for ordinal data and continuous data that do not follow a normal distribution. It always includes the median and represents the range within which the central 50% of data points lie. It is calculated as the dif-

**Table 1.** Graphical presentation of data: examples

| Qualitative data | Quantitative data |
|---|---|
| Pie chart | Line diagram |
| Bar chart | Histogram |
| Pareto chart | Frequency polygon |
| | Distribution curve |
| | Box plot |
| | Scatter plot |
| | Survival curve |

ference between the third quartile and the first quartile. The third quartile marks the 75th percentile, and the first quartile marks the 25th percentile. Because the interquartile range excludes extreme values, it is preferred over the range in many clinical applications. For instance, Zdravković et al. reported body weight, height, and body mass index as median and interquartile range in **Table 1** of their article [14].

The variance and standard deviation are key statistical measures used to describe data on an interval or ratio scale, particularly when the data follows a normal distribution. Variance represents the average squared deviation of individual values from the mean, while standard deviation, the most commonly used measure of variability, is mathematically derived as the square root of variance. In **Table 1** of the study by Krishnaveni et al., lipid profile data of patients are presented using mean and standard deviation [15].

While measures such as range, interquartile range, variance, and standard deviation express variability in the same units as the measured characteristic, they are not suitable for comparing the variability across characteristics with different units. In contrast, the coefficient of variation is a unit-free measure that allows such comparison (e.g., newborn body weight versus newborn body length). Defined as the ratio of standard deviation to the mean, it is typically expressed as a percentage. For instance, in **Table 1** of the study by Schmidt et al., glycemic control data are reported using the coefficient of variation [16]. Generally, a coefficient of variation of 30% or lower indicates statistical homogeneity, while values exceeding 30% suggest heterogeneity [17, 18].

*Measures of distribution shape*

Data distributions vary in shape, with normal distribution being the most significant for continuous variables [13]. Many biological processes and statistical analyses assume normality, graphically represented by a symmetric, bell-shaped curve in which the mean, median, and mode are identical **(Figure 2A)** [9].

Skewness and kurtosis are used to assess and describe the shape of distribution **(Figures 2 and 3)** [9].

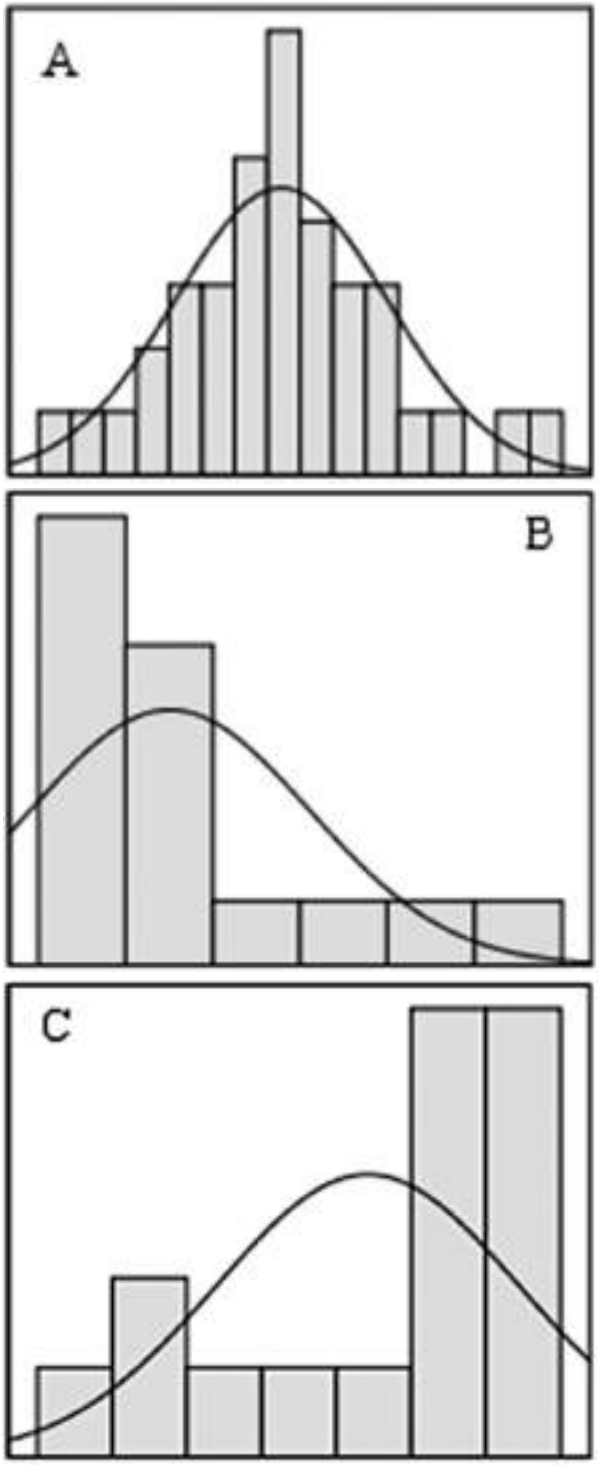


**Figure 2.** Distribution shape according to symmetry: A. normal (symmetric); B. positive skewed (asymmetric); C. negative skewed (asymmetric)

Skewness measures asymmetry in data distribution. A positively skewed distribution (right-skewed) occurs when the mode and median are less than the mean, shifting the peak leftward, with most values concentrated on the lower end and a longer right tail **(Figure 2B)**. Conversely, a negatively skewed distribu-

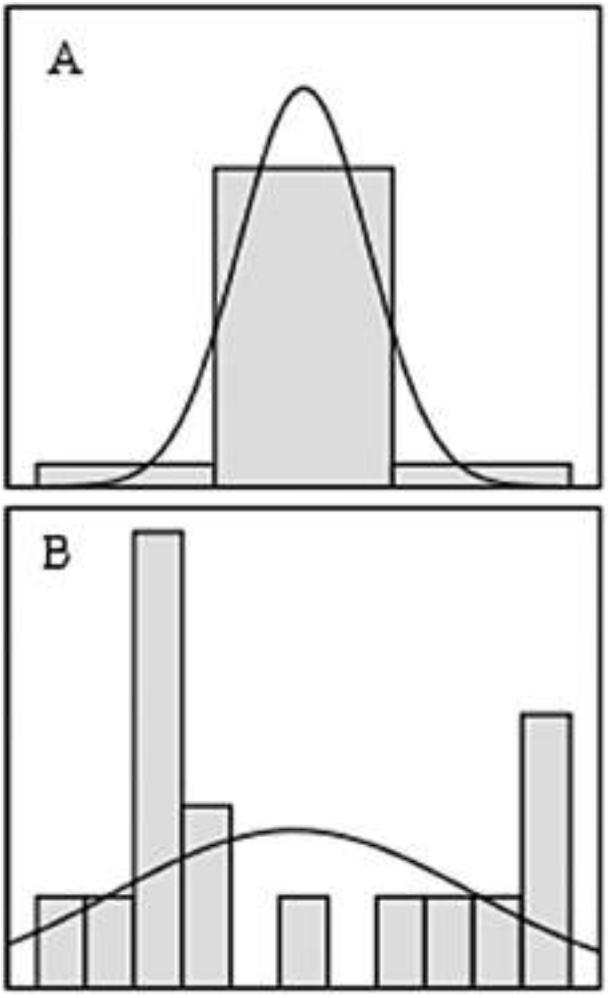


**Figure 3.** Distribution shape according to height and peak sharpness: A. positive kurtosis; B. negative kurtosis

tion (left-skewed) arises when the mode and median exceed the mean, shifting the peak rightward, with most values higher and a longer left tail **(Figure 2C).**

When skewness is approximately zero, the distribution is symmetric. In clinical studies, perfect symmetry is rare. A skewness range of -1 to +1 suggests minor deviation from normality, though values between -2 to +2 are often considered acceptable [17].

Kurtosis describes the height and sharpness of the distribution's peak. A positive kurtosis value indicates a high, narrow peak, while a negative value signifies a flatter, wider distribution **(Figure 3).**

As with skewness, kurtosis values between -1 and +1 suggest minor deviations from normality, though a range of -2 to +2 is generally acceptable [17].

*Tabular and graphical data presentation*

Once data have been collected and summarized, they should be presented clearly and concisely. This is typically achieved using tables and graphs. Tables provide the most comprehensive data representation and can be categorized by content (simple, complex, or combined) and purpose (reference and analytical). Graphs visually supplement tables rather than replace them. The choice of graphical representation depends on data type **(Table 1)** [9, 19]. Commonly used visualizations include histograms, bar charts, line charts, scatter plots, and box plots [20].

## Conclusion

Statistics are fundamental to clinical research and essential for interpreting scientific literature. While an in-depth understanding of complex mathematical formulas is not required, researchers and clinicians must grasp key statistical concepts, including variable classification, data, scales of measurement, descriptive and inferential statistics.

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# CASE REPORTS
# *PRIKAZI SLUČAJEVA*

## LARGE BOWEL OBSTRUCTION DUE TO METASTASIS OF PANCREATIC CANCER – CASE REPORT AND LITERATURE REVIEW

## *OPSTRUKCIJA DEBELOG CREVA IZAZVANA METASTAZOM KARCINOMA PANKREASA – PRIKAZ SLUČAJA I PREGLED LITERATURE*

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Case report
*Prikaz slučaja*
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**Abstract**

**Introduction**. Pancreatic cancer is among the most aggressive malignancies, with a poor prognosis. The liver, peritoneum, lungs, and distant lymph nodes are the most common metastatic sites. However, metastasis of pancreatic cancer to the large bowel is extremely rare. **Case Report.** A 48-year-old male with pancreatic cancer underwent radical pancreatosplenectomy in August 2022, accompanied by subtotal gastrectomy, partial resection of the transverse colon, and resection with reconstruction of the splenic vein. He subsequently received six cycles of adjuvant therapy based on the 5-fluorouracil/Leucovorin protocol, which concluded in February 2023. Routine follow-ups revealed multiple liver metastases by June 2023. First-line systemic treatment with the mono-Gemcitabine protocol was initiated, but disease progression occurred after three cycles. The patient then transitioned to second-line therapy with the De Gramont/Cisplatin protocol. During the second cycle, he developed intestinal obstruction necessitating emergency surgery, during which a sigmoidostomy was performed. Intraoperative biopsy of a tumor mass in the sigmoid colon confirmed metastasis of the previously operated pancreatic ductal adenocarcinoma into the colonic wall. **Conclusion.** Metastasis of invasive ductal pancreatic adenocarcinoma to the colon wall, causing intestinal obstruction, is an extremely rare occurrence, with only a few cases documented in the literature. Histopathological analysis of any colonic mass in patients with a history of pancreatic ductal adenocarcinoma is crucial to differentiate between primary colorectal cancer and metastatic lesions originating from pancreatic cancer.

**Key words**: Intestinal Obstruction; Colon; Colon, Sigmoid; Pancreatic Neoplasms; Neoplasm Metastasis

**Sažetak**

**Uvod.** Karcinom pankreasa je jedan od najagresivnijih oblika malignih bolesti sa lošom prognozom. Najčešća mesta metastaza karcinoma pankreasa su jetra, peritoneum, pluća i udaljeni limfni čvorovi. Metastaza karcinoma pankreasa u debelo crevo je izuzetno retka pojava**. Prikaz slučaja.** Pacijent, muškog pola, star 48 godina koji boluje od karcinoma pankreasa bio je podvrgnut operaciji u avgustu 2022. godine kada je načinjena radikalna pankreatosplenektomija sa suptotalnom gastrektomijom, parcijalnom resekcijom transverzalnog kolona, resekcijom i rekonstrukcijom lijenalne vene. Pacijent je primio adjuvantnu terapiju po protokolu 5-fluorouracil/*Leucovorin* u šest serija do februara 2023. godine i redovno je bio praćen do pojave više metastaza u jetri do juna 2023. godine. Počeo je prvu liniju sistemskog lečenja po mono-*Gemcitabin* protokolu u tri serije, nakon čega je došlo do progresije bolesti. Pacijent je nastavio sa drugom linijom lečenja po *De Gramont/Cisplatin* protokolu i dok je primao drugu seriju terapije razvio je crevnu opstrukciju. Načinjena je hitna operacija sa kreiranjem sigmoidostomije, a intraoperativno je uočena i bioptirana tumorska masa u sigmoidnom debelom crevu. Definitivni histopatološki nalaz ukazivao je na metastazu prethodno operisanog karcinoma pankreasa u zid debelog creva. **Zaključak.** Metastaza invazivnog duktalnog adenokarcinoma pankreasa u zid debelog creva, sa posledičnom crevnom opstrukcijom, izuzetno je redak entitet sa samo nekoliko slučajeva opisanih u dostupnoj literaturi. Svaku masu debelog creva kod pacijenata sa istorijom pankreasnog adenokarcinoma treba patohistološki analizirati kako bi se razlikovao primarni kolorektalni karcinom i metastaza koja potiče od karcinoma pankreasa.

**Ključne reči**: opstrukcija creva; debelo crevo; sigmoidni kolon; karcinom pankreasa; metastaza

### Introduction

Pancreatic cancer is one of the most aggressive malignant diseases, characterized by a poor prognosis. Pancreatic ductal adenocarcinoma (PDAC) accounts for over 85% of all pancreatic cancer cases and represents the most common form of this malignancy [1]. The disease is marked by a prolonged asymp-

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***Abbreviations***

PDAC – pancreatic ductal adenocarcinoma
MRI – magnetic resonance imaging
CT – computed tomography
AP – anterior-posterior
LL – laterolateral
CC – craniocaudal
5FU/LV – 5 fluorouracil and leucovorin
HE – hematoxylin eosin
WBC – white blood cells
CRP – C-reactive protein
IHC – immunohistochemistry
CK – cytokeratin

tomatic course and early metastasis to distant organs, making its progression highly unpredictable. The liver, peritoneum, lungs, and distant lymph nodes are the most common metastatic sites, while rarer locations include the bones, kidney, and skin [2]. Metastasis to the large intestine is an extremely rare occurrence, with only a few cases reported in the literature. Documenting such cases is essential to enhance understanding of PDAC's metastatic behavior and its clinical implications.

Acute abdomen is a clinical entity characterized by sudden and severe abdominal pain. The differential diagnosis is broad, encompassing various potential causes, which can complicate diagnosis and management. In patients with a history of malignancy, acute abdomen poses a significant challenge, requiring a multidisciplinary approach to achieve optimal care.

## Case Report

This report details the case of a 48-year-old male undergoing treatment for pancreatic cancer. The patient had a significant history of smoking (one pack daily for 30 years) and regular alcoholic consumption. His past medical history included childhood epilepsy, and there was no family history of malignancy.

Clinical suspicion of pancreatic cancer arose in July 2022 after the patient underwent magnetic resonance imaging (MRI) of the abdomen due to severe epigastric pain radiating to the back and unintentional weight loss of 10 kg over three months. Radiological findings revealed a poorly defined, partially cystic soft-tissue mass located at the transition line between the body and tail of the pancreas, measuring approximately 47x55x48 mm (APxLLxCC). The mass appeared to infiltrate the splenic vein, the greater curvature of the stomach, and possibly a part of the transverse colon. A multidisciplinary team deemed the tumor resectable, and radical surgical treatment was performed in August 2022. The procedure included a radical anterograde modular pancreatosplenectomy, subtotal gastrectomy and "Roux-en-Y" reconstruction, resection

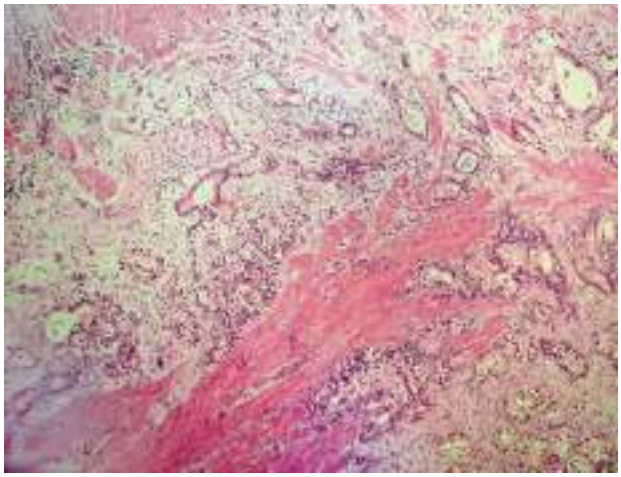

**Figure 1.** Moderately differentiated invasive pancreatic ductal adencarcinoma with lymphovascular and perineural invasion (HE, 40x)

and reconstruction of the splenic vein, and resection of the transverse colon with T-T anastomosis. Histopathological examination confirmed a moderately differentiated invasive ductal adenocarcinoma with lymphovascular and perineural invasion **(Figure 1).** Malignant infiltration was found in 2 of 25 resected locoregional lymph nodes. The disease was staged as pT3N1, corresponding to stage IIB per the American Joint Committee on Cancer.

Given the disease stage, the multidisciplinary oncology team indicated adjuvant therapy with six cycles of 5-fluorouracil and leucovorin (5FU/LV) over three months. The patient completed treatment by February 2023 without delays or significant side effects. Follow-up imaging in March 2023, including chest computed tomography (CT) scan and abdominal MRI showed no signs of disease dissemination or local recurrence.

In June 2023, routine MRI of the abdomen detected multiple focal lesions in the liver with metastatic characteristics, localized in the following segments: S8/S4a (12 mm), S2 (12 mm) and subcapsular in S5 (10 mm). Chest CT findings were negative for metastasis. Due to the progression of the disease, first-line treatment with mono-Gemcitabine protocol was initiated, and the patient received three cycles by September 2023 without side effects and complications. However, subsequent abdominal MRI showed disease progression, with enlargement of the liver lesions and new retroperitoneal lymphadenomegaly, with the largest one located in the coeliac trunk area with a short diameter of 10.5 mm. Second-line treatment with 5-fluorouracil and cisplatin (De Gramont/CDDP protocol) was started.

The first cycle of the second-line treatment proceeded without any adverse events. Two weeks after

the initial chemotherapy session, the patient was routinely hospitalized for the second cycle but reported abdominal discomfort upon admission. Laboratory findings before hospitalization were satisfactory, and the initial clinical examination revealed no anomalies. The patient was administered a nonsteroidal painkiller, and the planned chemotherapy was initiated. On the second day of chemotherapy, the patient experienced an acute exacerbation of his abdominal pain and called for urgent medical assistance.

His clinical presentation included diffuse abdominal pain resistant to pain relief medication, nausea, persistent vomiting, and the absence of stool and gas passage. Clinically, the patient appeared pale, with unstable vital signs. Abdomen examination showed absence of peristalsis, metallic high-pitched bowel sounds in the lower left quadrant, distention, meteorism, and diffuse tenderness to superficial and deep palpation, with clinical signs of peritoneal irritation.

Laboratory test revealed a significantly elevated white blood cell (WBC) count of 14.36 x $10^9$/L (reference range: 4-10.0 x $10^9$/L), primarily due to an elevated neutrophil count (absolute neutrophil count 11.77 x $10^9$/L; reference range: 2-7.0 x $10^9$/L), along with a high level of C-reactive protein (CRP 193.7 mg/L; reference value: <5 mg/L). Combined with his unstable vital sings, these findings indicated an acute inflammatory response. An abdominal X-ray demonstrated multiple air-fluid levels without sings of pneumoperitoneum, indicative of bowel obstruction without bowel perforation.

The oncology surgeon on duty was consulted and, after reviewing the patient's medical history, transferred him from the Department of Differential Oncology Treatment to the Department of Oncological Surgery. Emergency surgery was performed the following day. Intraoperatively, multiple metastatic deposits were found in the abdominal cavity, with severe distention of both the small and large intestines. Complete luminal obstruction of the distal sigmoid colon was caused by a tumor mass, while the proximal ileum was partially obstructed due to external compression from peritoneal metastasis. The sigmoid colon was mobilized, a loop sigmoidostomy was created, and the tumor mass was biopsied. Additionally, the subocclusive segment of the ileum was resected, followed by an L-L ileo-ileo anastomosis. Histopathological analysis of the sigmoid tumor confirmed metastasis of previously diagnosed ductal adenocarcinoma of the pancreas **(Figure 2).** Postoperatively, the patient's general condition improved, and the planned systemic treatment regimen resumed. He received a total of five cycles of chemotherapy by February 2024. At a follow-up in March 2024, abdominal MRI revealed persistent small bowel distention due to progressing peritoneal carcinomatosis. However, the liver metastases in segments S2, S5, and S8 showed regression (12 mm to 8 mm, 12 mm to 9 mm, 10 mm to 9 mm, respectively). A CT scan of the chest indicated newly developed thrombosis in the intralobar pulmonary arteries on the right and in individual branches for the left basal lobe. Following this outpatient follow-up, the patient ceased attending regular visits and hospitalizations for continued differential oncology treatment.

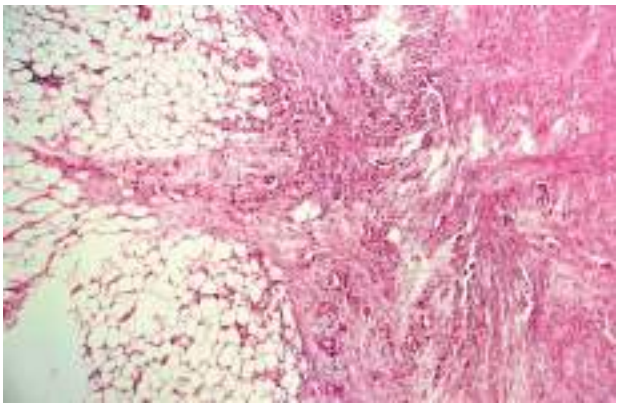

**Figure 2.** Metastasis of moderately differentiated invasive ductal adencarcinoma infiltrating sigmoid colon wall (HE, 40x)

## Discussion

This case highlights the rare occurrence of pancreatic ductal adenocarcinoma (PDAC) metastasizing to the colonic wall, resulting in intestinal obstruction. To the best of the authors' knowledge, only a limited number of such cases have been reported cases in the literature.

Pancreatic ductal adenocarcinoma accounts for more than 85% of all pancreas cancer cases [1]. It is one of the most aggressive malignancies, with a 5-year survival rate of less the 5% and a median survival of 17 to 23 months. In the absence of treatment for metastatic disease, life expectancy is typically less than three months [3]. The incidence of PDAC peaks in the seventh decade of life, ranking as the 11th most common malignancy globally and the 7th leading cause of cancer-related deaths [4]. Its poor prognosis is underscored by the near equivalence of its annual incidence and mortality rates.

The etiology of PDAC remains unclear, likely multifactoral, with several identified risk factors. These are categorized into non-modifiable factors such as age, gender, race, family history, and hereditary genetic syndromes [5], and modifiable factors, including smoking, alcohol consumption, type 2 diabetes, obes-

ity, and chronic pancreatitis. Men are twice as likely to develop pancreatic cancer compared to women of the same age [4]. Hereditary pancreatic cancers account for about 10% of all cases, one-third of which are caused by hereditary genetic syndromes and two-thirds belong to the group of family cancers with a positive family history. Multiple studies have identified smoking as the leading risk factor for developing pancreatic cancer not only for passionate smokers but also for people smoking several cigarettes a day, and even for passive smokers [6]. Alcohol consumption was also studied thoroughly, emphasizing its role in carcinogenesis of pancreatic cancer, especially in heavy-drinkers (>60 g of ethanol per day) [7]. Type 2 diabetes is the third most significant modifiable risk factor that increases the risk 1.5- to 2-fold, with most cases manifesting 2-3 years before the initial diagnosis [8]. Obesity has shown to increase risk of developing pancreatic cancer by 2-fold. Increase in body mass index by 5 kg/m$^2$ was associated with a 12% greater risk of the disease [9]. Recent studies have revised the link between chronic pancreatitis and PDAC, indicating the highest cancer risk occurs shortly after diagnosis, emphasizing the need for close monitoring especially in the first year after diagnosis [10].

Surgical resection remains the only potentially curative treatment for PDAC [11]. However, more than 80% of cases are diagnosed in advance stages, precluding curative intervention. Approximately half of newly discovered PDAC cases present with metastatic disease. This is mainly due to its prolonged asymptomatic period and early propensity for distant spread. Evan after potentially curative resection followed by adjuvant chemotherapy, most patients will experience recurrence with a five-year survival rate of 25% [12]. Nevertheless, recurrence of pancreatic cancers, either as a local or metastatic disease, occurs even after R0 residual status in up to 80% of patients [12]. A retrospective study by Kovač JD, et al. estimated a mean recurrence time after radical surgical resection was 17.4 months [13]. PDAC, like most malignancies, can spread in any part of the body. The most common metastatic sites are liver (21-80%), lungs (7-28%), distant lymph nodes (18-25%), and peritoneum (11-23%). Less common sites of metastasis are bones, kidney and skin. Metastasis of pancreatic cancer to the intestinal wall is an extremely rare entity, with only few cases reported so far [14–25].

A detailed literature review using PubMed, by implementing the criteria "metastatic PDAC OR pancreatic ductal adenocarcinoma OR PC OR pancreatic cancer AND large intestine OR colon OR large bowel", identified 12 case reports meeting the above criteria, which are presented in **Table 1.**

The first documented case of large bowel obstruction due to metastasis of pancreatic cancer was reported by Tresadern C. John in 1981 [14]. This case laid the groundwork for subsequent descriptions of this rare clinical phenomenon. Analysis of the available literature suggests a significant rise in interest over the past decade, with an increasing number of cases being reported each year. This trend may be attributed to the introduction of novel therapeutic regimens that have extended the overall survival of pancreatic cancer patients, thereby allowing more time for such metastases to develop. Additionally, advancements in radiology and pathology have likely improved diagnostic accuracy and efficiency, contributing to the identification of more cases.

The mean age at diagnosis of intestinal obstruction due to PDAC metastasis was 68 years, consistent with the epidemiological data, indicating that the disease incidence is highest in the seventh decade of life [4]. The youngest recorded patient was 45 and the oldest was 91 years old. In terms of gender, there were seven men and five women, suggesting that the male sex is more likely to suffer from this disease compared to female [1, 4].

The clinical presentation at diagnosis varied, with abdominal pain and constipation being the dominant ones. In some cases, constipation preceded the onset of abdominal pain [16, 19, 24]. Unintentional weight loss and appetite loss [15, 20, 23, 25] were also frequently reported, which was expected as that these are the most common manifestation of malignant diseases, especially pancreatic cancer. These nonspecific symptoms overlap with those of primary gastrointestinal malignancies, complicating the diagnosis.

Regarding the localization of PDAC metastases in the large bowel, they were predominantly found on the left side of the colon, particularly in the sigmoid region. This localization complicates the differentiation between pancreatic cancer metastases and primary colon cancer, as primary malignancies are also more commonly observed on the left side of the colon. In all reported cases of intestinal obstruction, the initial assumption was that the obstruction was caused by a primary colon tumor. However, postresection histopathological analysis confirmed the presence of PDAC metastasis in the colon. While most cases involve a single metastasis site, some reports documented multiple metastatic sites [18, 20].

The analysis of **Table 1** reveals a higher incidence of synchronous presentations of pancreatic cancer and colonic metastases. In these cases, the primary tumor manifested with a nonspecific clinical symptoms until the onset of intestinal obstruction. The synchronous discovery of the primary tumor and metastasis is like-

**Table 1.** Comprehensive Overview of Metastatic PDAC to the Large Intestine: Case Summaries

| Author | Age/ Gender | Manifestation | PDAC Diagnosis history | Histopathology (Primary tumor) | Metastasis location | Histopathology (Metastatic PDAC) | Treatment |
|---|---|---|---|---|---|---|---|
| Tresadern. (1981) [14] | 68/M | Colicky abdominal pain and alternating constipation and diarrhea for 5 weeks | synchronous | N/A | Transverse colon | N/A | Palliative care |
| Bellows et al. (2009) [15] | 45/M | Several months of severe epigastric pain and unintentional weight loss | synchronous | N/A | Ascending colon | CA 19-9+, EMA+ and CEA+, CK7 -, CK20 - CDX2 - | N/A |
| Ogu et al. (2012) [16] | 85/F | One week obstipation and intermittent abdominal pain | post-pancreaticoduodenectomy 24 months prior | Stage IIA | Mid sigmoid colon | Strong CK7 + and weak CK20 +, CA 19-9+ | Hartmann's operation with adjacent lymphadenectomy |
| Inada et al. (2013) [17] | 62/M | Abdominal distension and pain | Pancreatoduodenectomy 7 years prior | pT2N1M0 stage IIB | Ascending colon | Strong CK7+ and CK20 - | Right hemicolectomy with adjacent lymphadenectomy |
| Kim et al. (2015) [18] | 64/M | Diffuse abdominal pain for 2 weeks | Distal Pancreatectomy 2 years prior | pT3N0M0 stage IIA | Ileocecal valve | Strong CK7+ and CK20 - | Right hemicolectomy |
| Kelley et al. (2016) [19] | 67/F | Four day of worsening abdominal pain and ten day Obstipation | synchronous | N/A | Distal sigmoid colon and rectum | N/A | Excision of the obstructed bowel and end colostomy |
| Gizzi et al. (2017) [20] | 70/F | Progressive weight loss and reduction of appetite | synchronous | N/A | Transverse and descendent colon | Strong CK7+ and CK20 - | N/A |
| Nogueira et al. (2018) [21] | 60/M | Low abdominal pain for two months | synchronous | N/A | Sigmoid colon | CK7+ and CK20 -, CDX2 - | Resection of the sigmoid tumor and colostomy placement after perforation |
| Miyasaka et al. (2018) [22] | 63/M | Abnormal laboratory tests (elevated CRP 3 months post operation), later abdominal pain | Pancreatoduodenectomy (R0 resection) after neoadjuvant therapy | Poorly differentiated PDAC pT2N0M0 stage IB | Transverse colon and jejunum | Poorly differentiated PDAC | Extirpation of the tumor mass |
| Kahl et al. (2019) [23] | 91/F | Unintentional weight loss, constipation and nausea | synchronous | N/A | Sigmoid colon | Well differentiated PDAC CK7+ and CK20 -, CDX2 - | Palliative resection of the sigmoid with end colostomy |
| Park et al. (2019) [24] | 73/F | Lower abdominal pain radiating in the back and obstipation for 10 days | synchronous | Moderately differentiated PDAC within a desmoplastic stroma CK7+ and CK20 – Stage IV | Sigmoid and descendent colon | Moderately differentiated PDAC pT3N2 CK7+ and CK20 -, CDX2-, SATB2 - | Subtotal colectomy and ileostomy |
| Meng et al. (2023) [25] | 65/M | Lower abdominal pain and unintentional weight loss | synchronous | Stage IV PDAC Strongly CK7+ and CK20 - | Sigmoid colon | Strongly CK7+ and CK20 - | Systemic treatment with mono Gemcitabine and Nab-paclitaxel |

Legend: PDAC - Pancreatic Ductal Adenocarcinoma; N/A - Not Available; M - male; F - female; IHC - Immunohistochemistry; CA 19-9 - Carbohydrate Antigen; EMA - Epithelial Membrane Antigen; CEA - Carcinoembryonic Antigen; CK 7/20 - Cytokeratin; CDX2 - Caudal-Type Homeobox gene, CRP - C-Reactive Protein; SATB2 - Special AT-rich Sequence-Binding Protein 2

ly due to the unpredictable biological behavior of pancreatic cancer, characterized by its propensity for early and distant metastases, even when the pancreatic tumor is relatively small and subclinical. Conversely, the occurrence of metachronous PDAC metastasis in the colon varied significantly, with timelines ranging from a few months [22] to several years [17] following the radical resection of the primary tumor.

Case reports on this topic emphasize the importance of additional histopathological diagnostics, particularly immunohistochemical (IHC) analyses, to reliably differentiate pancreatic cancer metastases from primary colon cancer. The most commonly utilized IHC markers in these cases are cytokeratin (CK) 7 and CK20, where CK7-positive and CK20-negative findings indicate an extraintestinal origin of the tumor in the bowel [16, 18, 20]. IHC analyses are especially beneficial in cases of synchronous presentation of pancreatic cancer and colon tumor changes. Furthermore, the presence of tumor cells in the submucosa without mucosal invasion, combined with the absence of precursor lesions such as adenomas or serrated polyps, strongly support the metastatic origin of colonic tumor changes [14].

Therapeutic strategies in most reported cases have involved palliative resection of the tumor mass and/or the creation of a protective stoma. Since ileus is a medical emergency, it requires prompt intervention to preventing fatal outcomes. Notably, the case described by Meng et al. [25] highlights systemic therapy as a viable treatment option for this clinical entity. The authors underscore the importance of achieving a preoperative diagnosis, emphasizing that in cases where PDAC metastases in the colon do not result in mechanical obstruction, systemic therapy may serve as the primary treatment modality.

## Conclusion

Metastasis of invasive ductal pancreatic adenocarcinoma to the colonic wall with subsequent intestinal obstruction is an extremely rare clinical entity. Its diagnosis and management require a multidisciplinary approach, with treatment plans tailored to the individual patient. In cases of bowel obstruction in patients with a history of ductal pancreatic adenocarcinoma, metastases in the colonic wall should be considered, and any tumor changes in the colon should undergo thorough histopathological evaluation to differentiate between primary colorectal cancer and metastasis originating from pancreatic cancer.

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# VULVAR MALIGNANT MELANOMA – CASE REPORT

## *MALIGNI MELANOM VULVE – PRIKAZ SLUČAJA*

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Case report
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**Abstract**

**Introduction.** Vulvar carcinoma is a rare gynecological malignancy, accounting for 0.6 percent of all female cancers. **Case Report.** A-76-year-old woman presented with a tumorous lesion in the lower third of the left labia majora and minora, measuring approximately 25 mm. A multifocal biopsy was conducted, and pelvic magnetic resonance imaging revealed slight enlargement of a left inguinal solid lymph node. The patient underwent a left hemivulvectomy with inguinofemoral lymphadenectomy. Histopathological analysis confirmed a malignant lentiginous tumor, and inguinofemoral lymphadenectomy revealed metastatic malignant melanoma. Despite a negative histopathological finding of the contralateral side during the initial biopsy, the patient returned within three months with a 9-mm mucosal nodular type melanoma on the lower third of the right labia majora. A wide excision of the vulva was subsequently performed. Following consultation with a multidisciplinary tumor board, adjuvant immunotherapy with Pembrolizumab (200 mg per cycle, 9 cycles) was initiated. **Conclusion.** Vulvar malignant melanoma is rare, aggressive, and unpredictable tumor that predominantly affects women in later life. It is associated with a high recurrence rate and a poor overall prognosis.

**Key words:** Vulvar Neoplasms; Melanoma; Neoplasm Metastasis; Magnetic Resonance Imaging; Gynecologic Surgical Procedures; Chemotherapy, Adjuvant

**Sažetak**

**Uvod.** Karcinom vulve je retko ginekološko oboljenje sa učestalošću od 0,6 procenata svih karcinoma kod žena. **Prikaz slučaja.** Sedamdesetšestogodišnja žena je upućena zbog tumorske promene lokalizovane u donjoj trećini velikih i malih usana, sa leve strane, promera oko 25 mm. Urađena je multifokalna biopsija. Magnetnom rezonancijom karlice uočeno je blago uvećanje ingvinalnog limfnog čvora sa leve strane. Načinjena je levostrana hemivulvektomija sa ingvinofemoralnom limfadenektomijom. Patohistološki nalaz potvrđuje prisustvo malignog lentiginoznog tumora. Ingvinofemoralnom limfadenektomijom dokazano je prisustvo metastatskog malignog melanoma. I pored urednog patohistološkog nalaza kontralateralne strane vulve, dobijenog multifokalnom biopsijom, za manje od tri meseca, pacijentkinja se ponovo javlja sa de novo tumorskom promenom nodularnog tipa melanoma promera oko 9 mm, lokalizovanom u donjoj trećini velike usne sa desne strane. Urađena je široka lokalna ekscizija vulve. Onkološka komisija je indikovala adjuvantnu imunoterapiju pembrolizumabom, 200 mg po seriji, devet serija. **Zaključak.** Maligni melanom vulve je redak, nepredvidiv i agresivan tumor koji se najčešće javlja kod žena starijeg životnog doba sa visokom stopom recidiva i ukupno lošom prognozom.

**Ključne reči:** tumori vulve; melanom; metastaza; magnetna rezonanca; ginekološke operativne procedure; adjuvantna hemoterapija

### Introduction

Vulvar carcinoma is a rare gynecological malignancy, accounting for approximately 0.6% of all female cancers [1–3]. Despite its rarity, the vulva represents the most common site for melanoma within the female genital tract, even though vulvar melanomas (VM) constitute a small fraction of both vulvar cancers and melanomas overall [4, 5]. VM is the second most common type of vulvar carcinoma after squamous cell carcinoma [6, 7]. While predominantly affecting white postmenopausal women, cases have been documented in younger individuals, with a median diagnostic age of 68 years [5]. Due to its rarity, treatment protocols for VM are largely extrapolated from those established for cutaneous melanomas. This report presents a case of malignant vulvar melanoma and discusses the associated management strategy.

### Case Report

A 76-year-old multiparous woman with a history of hypertension presented with a tumorous vulvar lesion, which she had noticed for approximately one year. There was no family history of malignancy. Ethical approval for this study was obtained on September 19, 2024, under protocol number 00-336 from the Ethics Committee of the University of Novi Sad, Faculty of Medicine Novi Sad, Serbia.

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***Abbreviations***

| | |
|---|---|
| VM | – vulvar melanoma |
| MRI | – magnetic resonance imaging |
| MDT | – multidisciplinary meeting |
| HPF | – high power field |
| VMM | – vulvar malignant melanoma |
| AJCC | – The American Joint Committee on Cancer |
| FIGO | – The International Federation of Gynecology and Obstetrics |
| GOG | – The Gynecologic Oncology Group |

On clinical examination, the vulva displayed a tumorous lesion with an uneven surface and irregular shape, characterized by exophytic growth in the lower third of the left labia majora and minora. The lesion measured approximately 25 mm and showed hyperpigmentation in certain areas **(Figure 1).** The vaginal vault and walls were smooth, with no evidence of pigmentation.

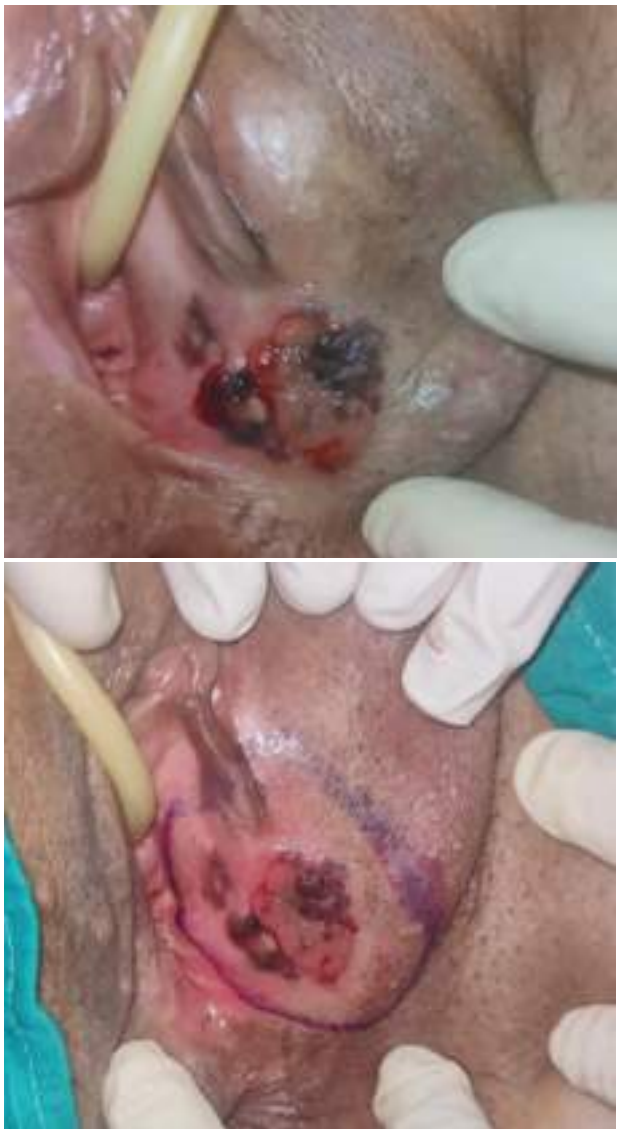

**Figure 1.** Macroscopic view of the initial vulvar tumor

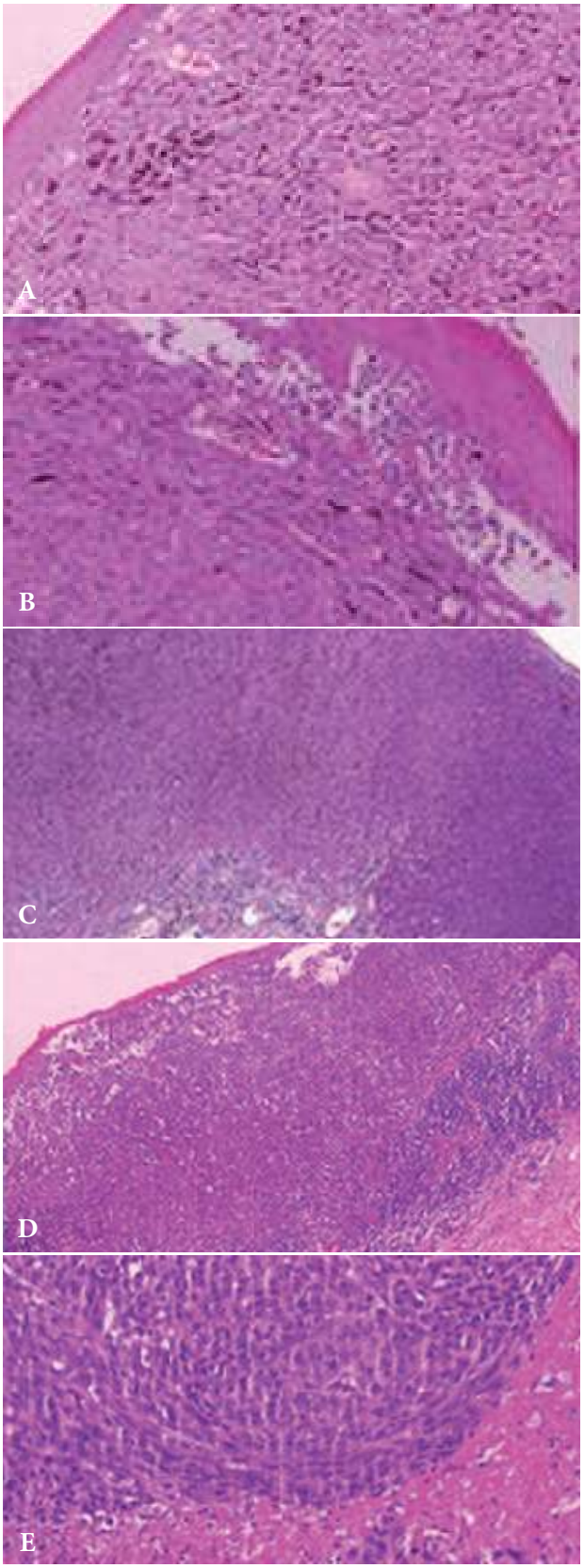


**Figure 2. A), B)** vulvar malignant melanoma after biopsy, HE, 10x **C), D)** vulvar malignant melanoma (mucosal lentiginous melanoma) after resection, HE, 5x **E)** Vulvar malignant melanoma after resection, HE, 20x.

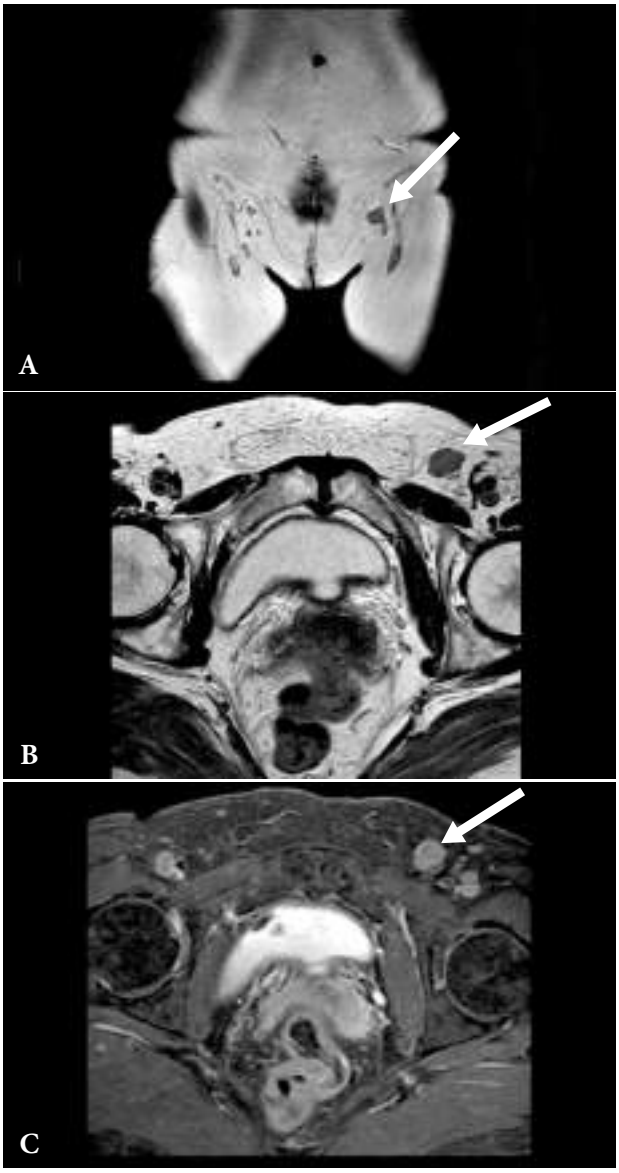


**Figure 3.** Pelvic MRI showing a suspicious, pathologically altered left inguinal lymph node (marked with arrow) in: A) T2W coronal plane, B) T2W axial plane and C) T2 SPAIR axial plane.

Multifocal biopsy revealed malignant cells infiltrating the left-sided vulvar tissue. These cells were arranged in solid sheets and clusters within the epidermis, dermis, and papillary dermis **(Figure 2).** The tumor consisted of epithelioid to spindled cells, with scattered intracytoplasmic melanin pigment and tumor-infiltrating lymphocytes. No lymphovascular or perineural invasion was observed. Biopsies from the contralateral vulvar side were negative for malignancy.

Pelvic magnetic resonance imaging (MRI) identified a mild enlarged, potentially pathologically altered left inguinal solid lymph node **(Figure 3).**

After a multidisciplinary (MDT) discussion and preoperative planning, the patient underwent a left hemivulvectomy and inguinofemoral lymphadenectomy. Suspicious superficial and deep left inguinal nodes were included in the resection and submitted for histopathological analysis.

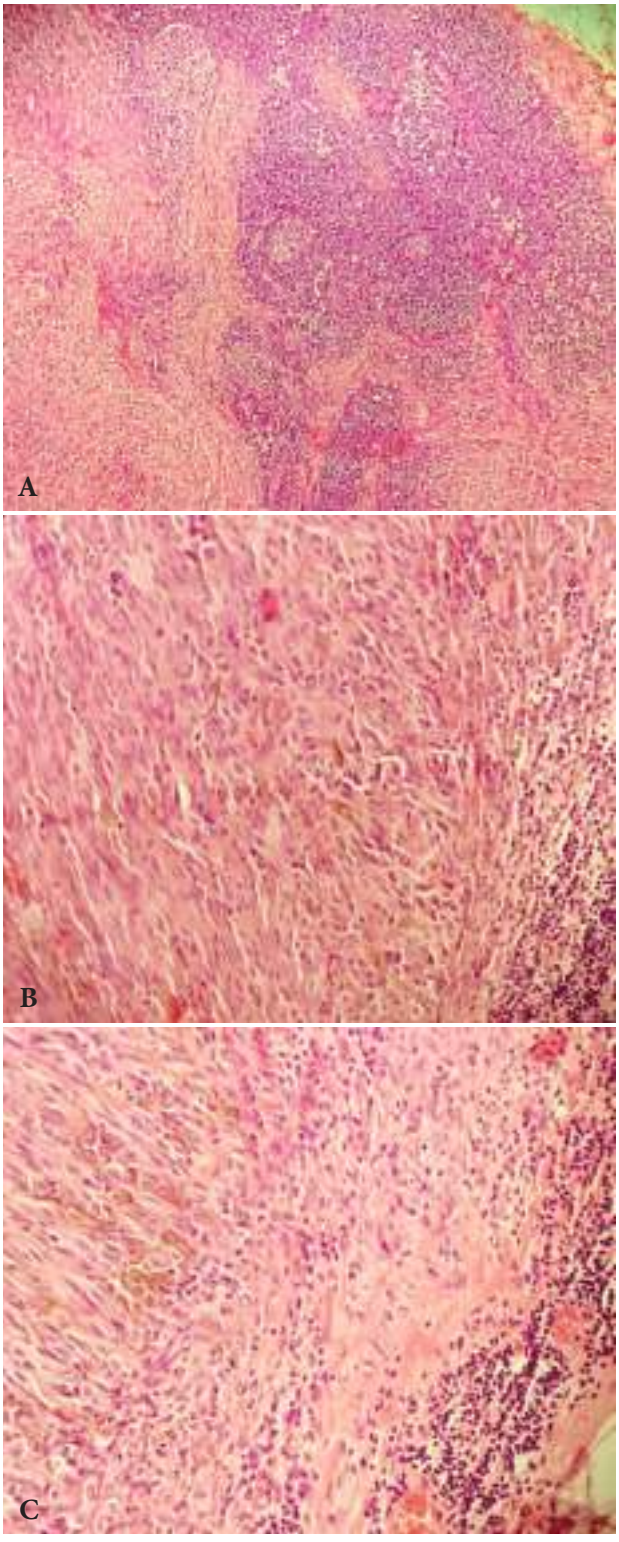


**Figure 4.** Melanoma metastases in the lymph node, **A)** HE, 5x, **B)** 20x, **C)** 20x

Histopathology revealed a malignant lentiginous tumor extending into the papillary and reticular dermis (Clark Level IV) with epidermal ulceration **(Figure 2).** The tumor exhibited a mitotic index of 13/10 high-power field (HPF) and a Breslow thickness of 1.5 mm. Brisk tumor-infiltrating lymphocytes were noted, but there was no evidence of perineural or lymphovascular invasion. The closest resection margin measured 10 mm. Inguinofemoral lymphadenectomy confirmed metastatic malignant melanoma in 3 of 6 lymph nodes **(Figure 4).** Immunohistochemical analysis showed HMB45+, Melan A+, AE1/AE3-, p40-. The final diagnosis was mucosal lentiginous melanoma, pT2b N2b M0, Stage IIIB.

Within three months of the initial surgery, the patient returned with a 9-mm tumor-like in the lower third of the right labia majora, despite the earlier contralateral biopsy findings being negative. MRI of the pelvis showed no pathological changed in the right inguinofemoral region; thus, lymphadenectomy was not performed. A wide local excision of the vulva was conducted. Histopathological analysis revealed Clark's Level IV involvement, with tumor extension into the reticular dermis **(Figure 5).** The tumor demonstrated a Breslow thickness of 2.5 mm with ulceration but no inguinal lymph node involvement. The mitotic index was 11/10 HPF, and the closest resection margin measured 12 mm. The diagnosis was mucosal nodular melanoma.

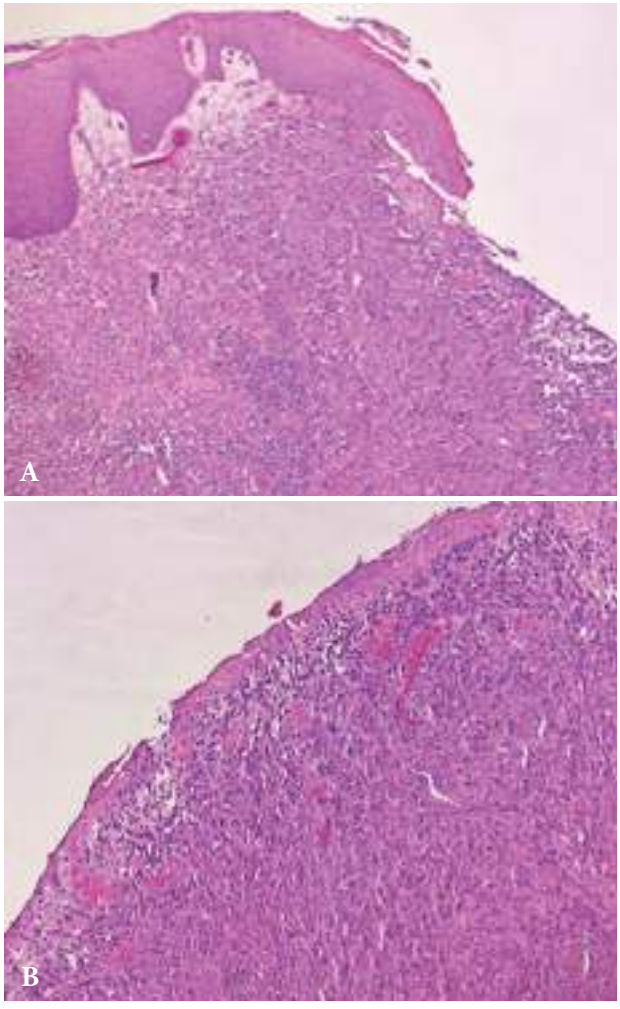


**Figure 5.** Vulvar malignant melanoma (mucosal nodular melanoma) after resection: **A)** HE, 5x, **B)** HE, 10x.

Further diagnostic examination, including MRI of the endocranium, computerized tomography (CT) of the chest, abdomen, and pelvis, and ultrasound of the neck, axilla, and inguinal regions, revealed no pathological lymph nodes. Testing for the BRAF V600 gene mutation was negative.

Based on the findings, the multidisciplinary tumor board indicated adjuvant immunotherapy with Pembrolizumab (200 mg per cycle, 9 cycles).

**Discussion**

Melanomas are malignancies originating from melanocytes, with over 90% arising in the skin. The pathophysiology of vulvar melanoma (VM) remains poorly understood; however, it is thought to develop de novo on the vulva, as chronic sun exposure and UV radiation damage are not associated with VM [8]. Chronic dermatoses, such as lichen sclerosus, have been suggested as potential risk factors [9].

The incidence of vulvar malignant melanoma (VMM) compared to cutaneous melanoma is approximately 1:17, and is associated with a high recurrence rate [3, 10]. Vulvar melanoma typically presents in older women, as highlighted in our case [5, 8].

Vulvar melanoma carries a significantly worse prognosis than cutaneous melanoma, with a five-year survival rate of less than 50% [11]. Research indicates that lymph node status and mitotic count play critical roles in determining outcomes [12]. Nagarajan et al. reported that a high mitotic index, as observed in our case, is associated with substantially poorer outcomes compared to a low mitotic index [13].

Although vulvar cancer can manifest with symptoms such as a vulvar lump, discomfort, bleeding, and itching, early-stage vulvar malignancies may present as asymptomatic or oligosymptomatic flat or raised pigmented lesions. A carefully planned biopsy remains the gold standard for diagnosis [3, 5, 7, 12, 14]. In addition to describing the anatomical location, we documented the lesion's position using the clock–face method, noting its distance from the midline and vaginal introitus, as recommended [10].

Differential diagnosis of VMM is often complex due to the overlapping clinical and pathological features of benign and malignant lesions [12, 15].

While advancements in dermoscopy have significantly improved the early diagnosis of cutaneous melanomas, its utility in vulvar melanoma diagnosis requires further validation.

For biopsy-confirmed vulvar melanomas, the American Joint Committee on Cancer (AJCC) staging system is preferred over the International Federation of Gynecology and Obstetrics (FIGO) system, which is used for vulvar squamous cell carcinoma. The Gynecologic Oncology Group (GOG)-73 study demonstrated that AJCC staging provides a more accurate survival prediction, a finding supported by recent population-based analyses [5, 12].

The AJCC 8th edition on melanoma staging and classification uses the Breslow thickness to determine the depth of invasion, providing a critical parameter for tumor staging under the traditional tumor-node-metastasis framework [16]. Although no universally accepted staging system exists for VM, the GOG recommends using the AJCC guidelines rather than FIGO [10].

Histological assessment of melanoma tumors with macroscopic data, and additional clinical diagnostic standards remain essential. While many histological subgroups may be clinically less significant, lentiginous and nodular melanomas – identified in this case – are the most common subtypes and warrant specific attention [17, 18].

Given the advanced stages at presentation, preoperative imaging is critical for surgical planning and delineating disease extent [10, 19]. In this case, pelvic MRI facilitated a comprehensive evaluation of the tumor.

The absence of standardized therapeutic guidelines for VM, coupled with its frequent presentation at metastatic or locally advanced stages, remains a significant challenge. As a result, treatment approaches often mirror those for cutaneous melanoma [18].

Surgical excision remains the cornerstone for vulvar melanoma management [10, 12, 18, 19]. Wide local excision with adequate safety margins is preferred, as radical excision has not demonstrated a significant therapeutic advantage [18, 20, 21].

Consistent with the National Comprehensive Cancer Network and European Society of Medical Oncology guidelines, our surgical margins for the lentiginous tumor with a Breslow thickness of 1.5 mm ranged from 1 to 2 cm. However, for the nodular melanoma with a Breslow thickness of 2.5 mm, we opted for narrower margins to preserve the functional integrity of midline structures, including the anus, urethra, and clitoris [1, 22, 23].

## Conclusion

Vulvar melanoma is a rare and aggressive malignancy with a high recurrence rate and poor overall prognosis. It predominantly affects women in latter decades of life. Biopsy remains the gold standard for accurate diagnosis given the overlapping features of benign and malignant tumors. Prognosis is largely determined by lymph node involvement and mitotic count. Surgical excision remains the primary treatment, offering effective local disease control and improving quality of life by minimizing morbidity.

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# FROM NEGLECT TO METASTASIS – A GIANT ABDOMINAL BASAL CELL CARCINOMA

# *ZANEMARIVANJEM DO METASTAZA – DŽINOVSKI ABDOMINALNI BAZOCELULARNI KARCINOM*

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Case report
*Prikaz slučaja*
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**Abstract**

**Introduction.** Basal cell carcinoma, or basalioma, is the most common type of skin cancer. It typically develops on sun-exposed areas such as the head and neck, but occurrences on the abdomen are rare. Basal cell carcinoma is characterized by slow progression and low risk of metastases due to early detection and treatment. As a result, giant basal cell carcinomas, exceeding 5 cm in diameter, are uncommon. **Case Report.** We present the case of a 66-year-old woman diagnosed with basalioma. A decade earlier, she noticed a small skin lesion on her abdomen that gradually enlarged. By the time she sought medical attention, the lesion had reached 20 x 30 cm, infiltrating the anterior abdominal wall, muscles, and peritoneum. Surgical management included tumor excision, the elevation of two large transposition myocutaneous flaps, and coverage of residual skin defects with free partial-thickness skin transplants. At the three-month postoperative follow-up, no signs of recurrence were observed. However, the patient missed the subsequent check-ups for personal reasons, resulting in delayed detection of a recurrence. Two and a half years later, clinical examination revealed a local relapse. Magnetic resonance imaging identified two ulcerative lesions, measuring 7 cm and 9 cm in diameter, connected by a bridge-like tissue formation infiltrating deeper structures, including the liver capsule and intestinal walls. At this advanced stage, surgical intervention was deemed unfeasible. **Conclusion.** Although basalioma is typically detected and treated early, neglected cases can result in giant lesions with significant local invasion, and even organ involvement. Educating patients on the importance of adherence to follow-ups is essential to prevent such adverse outcomes.

**Key words:** Abdominal Wall; Abdomen; Carcinoma, Basal Cell; Skin Neoplasms; Neoplasm Metastasis; Myocutaneous Flap; Recurrence; Medical Neglect

**Sažetak**

**Uvod.** Bazocelularni karcinom (bazaliom) najčešći je oblik karcinoma kože. Obično se javlja na područjima koja su izložena suncu, kao što su glava i vrat, dok je prednji trbušni zid retka lokalizacija po učestalosti. Bazaliom je poznat po sporom napredovanju i retkim pojavama metastaza usled ranog otkrivanja i lečenja. Zbog toga retko raste kao džinovski bazaliom sa prečnikom većim od 5 cm. **Prikaz slučaja.** Žena stara 66 godina javila se na pregled zbog tumora prednjeg trbušnog zida. Deset godina ranije primetila je malu leziju kože na stomaku koja je progresivno rasla. Kada se javila lekaru, dimenzije lezije su bile 20 x 30 cm, infiltrirala je prednji trbušni zid, mišiće i peritoneum. Tumor je hirurški uklonjen, korišćena su dva velika transpoziciona miokutana režnja, a slobodni transplantat parcijalne debljine kože je korišćen za prekrivanje zaostalog defekta kože. Tri meseca nakon operacije nije bilo znakova recidiva. Lični razlozi ometali su kasnije kontrolne preglede, što je dovelo do neprimećenog relapsa bolesti. Dve i po godine kasnije klinički pregled je pokazao lokalne recidive, dok su magnetnom rezonancijom identifikovane dve ulcerativne lezije, prečnika 7 i 9 cm, koje su bile povezane supkutano, stvarajući formaciju nalik mostu koja je probila kapsulu jetre i zidove creva. U ovoj fazi dalje hirurško lečenje nije bilo moguće. **Zaključak.** Uprkos mogućem ranom otkrivanju i uspešnom lečenju bazalioma, zanemareni slučajevi mogu se javiti sa lezijama koje postaju džinovske u prečniku, pa čak i zahvatati druge organe. Potrebno je edukovati pacijente o karcinomima kože, ali i važnosti komplijanse, jer to značajno doprinosi izbegavanju neželjenih ishoda.

**Ključne reči:** prednji trbušni zid; abdomen; bazocelularni karcinom; tumori kože; metastaza; miokutani režanj; recidiv; zanemareni medicinski slučaj

## Introduction

Basal cell carcinoma (BCC) is the most prevalent malignancy and the leading form of skin cancer [1]. Originating from the basal layer of the epidermis and adnexal structures, its primary etiological factor is ultraviolet (UV) radiation exposure. Individuals with fair skin, light-colored eyes, red hair, northern European ancestry, advanced age, childhood freckling, and a history of frequent sunburns are at heightened risk of developing this cancer [2]. Despite its high incidence, BCC typically has a favorable prognosis

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***Abbreviations***

BCC – basal cell carcinoma
UV – ultraviolet
GBCC – giant basal cell carcinoma
MRI – magnetic resonance imaging
NCCN – National Comprehensive Cancer Network

when identified and treated early [1]. In rare instances, BCC may grow to exceed 5 cm in diameter, classifying it as a giant basal cell carcinoma (GBCC), a condition accounting for approximately 0.5% of cases [3]. GBCC demonstrates aggressive biological behavior, infiltrating deep tissues, including dermis, bone, muscle, or cartilage, and may even metastasize, leading to a poorer prognosis [4]. Exceptionally, when a lesion surpasses 20 cm in diameter, it is classified as super giant basal cell carcinoma, underscoring its rarity and clinical significance [3]. The anatomical distribution of GBCC differs from typical BCC. While BCC predominantly affects the head and neck, GBCCs also occur on the trunk and upper extremities, often in areas less accessible for self-examination. Most patients present with GBCC around age 67, with a male predominance (2:1), and incidence peaks in those over 70 [5]. Treatment for GBCC typically involves surgical excision with wider margins (10 mm) to mitigate the significant risk of residual tumor (up to 68%) [5]. Deep excisions often require reconstructive techniques, including split-thickness graft, or local regional, or free flap to address the resulting defect [5]. Here, we report a case of a female patient in her seventh decade with a GBCC on the abdomen, an uncommon site. The lesion's size and the patient's lack of compliance during postoperative follow-up emphasize the critical importance of patient adherence to medical recommendations.

## Case Report

A 66-year-old woman presented to the outpatient department of the Clinic for Plastic and Reconstructive Surgery of the University Clinical Center of Vojvodina with a large abdominal skin lesion. She reported noticing a small reddish spot about ten years earlier, which gradually grew over time. The lesion, predominantly affected the anterior abdominal wall on the right side, exhibiting an exulcerative surface, punctate bleeding, foul odor, and purulent discharge at its center. The lesion measured approximately 20 x 30 cm and had multiple satellite lesions at its periphery **(Figure 1).** A partial biopsy and histopathological findings confirmed the diagnosis of BCC. Imaging studies, including ultrasound of the abdomen, inguinal, and axillary lymph nodes, as well as chest X-rays, revealed no signs of metastasis.

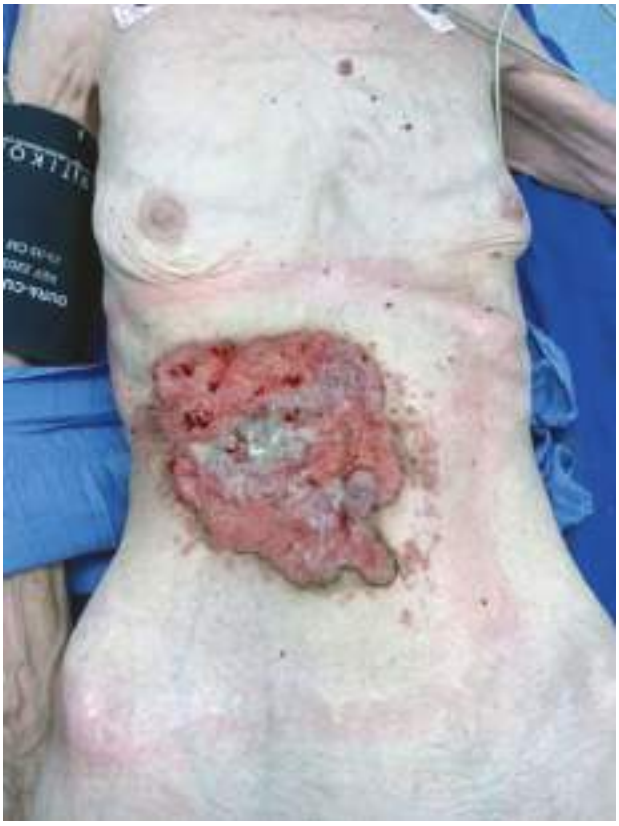

**Figure 1.** GBCC when first diagnosed

Surgical intervention involved complete excision of the tumor. Intraoperative findings showed infiltration of the anterior abdominal wall structures, including muscles and peritoneum. The peritoneum defect, measuring 10 x 8 cm, was repaired using a nylon mesh. Two large transposition myocutaneous flaps were raised, and the remaining defects were covered with free partial-thickness skin grafts. The surgery and postoperative recovery were uneventful. Histopathological analysis confirmed fat and muscle infiltration, with free lateral margins but close proximity to the deep margin. Adjuvant radiotherapy was not recommended by the oncology team. Three months postoperatively, the patient exhibited no signs of local recurrence or palpable regional lymph nodes. Follow-up imaging, including magnetic resonance imaging (MRI), ultrasound of the abdomen, inguinal, and axillary regions, and X-rays of the heart and lungs, showed no evidence of residual disease.

Despite initial follow-up, the patient missed subsequent appointments due to personal reasons. Two years later, relapse significant local recurrence was identified. Clinical examination revealed two ulcerative lesions, measuring 7 and 9 cm in diameter, along with a satellite lesion in the paraumbilical region **(Figure 2).** MRI demonstrated that the two ulcerative lesions formed a bridge-like structure in the deeper layer, disrupting

**Figure 2.** Local relapse two years post-op

the liver capsule and intestinal walls **(Figures 3A and 3B).** Additionally, a multilocular cystic tumor measuring 51 x 72 x 76 mm (AP x LL x CC) was identified in liver segments S4b and S5. The tumor had breached the liver capsule and was directly connected to the

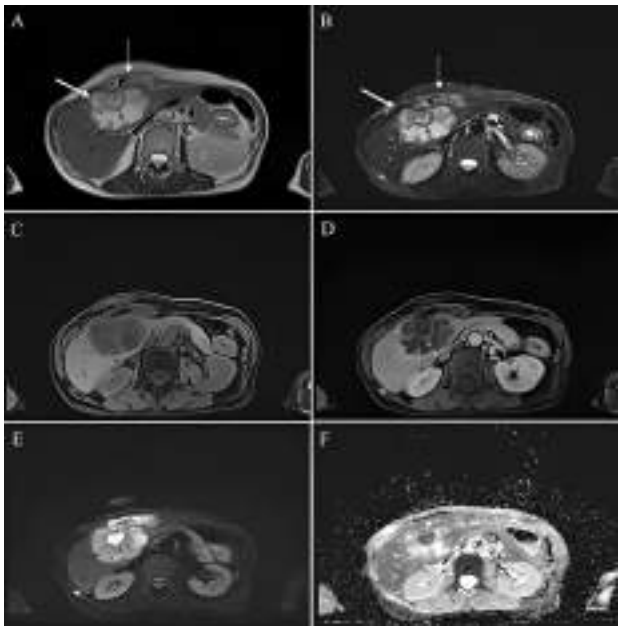

**Figure 3. A:** MRI demonstrating disruption of the liver capsule and **B:** connections with the anterior abdominal wall

ulcerative lesions on the anterior abdominal wall. Given the extent of disease progression, surgical intervention was deemed unfeasible.

**Discussion**

GBCCs are relatively rare, largely due to the widespread early treatment of BCCs that prevents tumors from reaching such large sizes. However, late-presenting cases of GBCC are still encountered. Several factors have been associated with the development of GBCC, including residence in rural areas, alcohol consumption, occupational exposure, psychophysical disorders, low socioeconomic and educational status, and insufficient social or family support [6].

Research suggests that female patients may have a higher propensity to neglect skin lesions [5]. While the mean age of GBCC patients is typically over 65, recent studies indicate that its occurrence is more common in individuals aged 75 and older [7]. The average duration of GBCC lesions is significantly longer than that of conventional BCCs, with reports indicating a mean duration of 109.7 months, suggesting that many patients may are aware of their lesions but disregard their potential severity [5]. The anatomical distribution of GBCC differs from that of conventional BCCs. Although the head and neck are the most common sites for BCCs, trunk involvement is rare, accounting for only 10% of cases. In contrast, GBCCs have a higher prevalence on the trunk, with an incidence of approximately 30% [4]. An Italian multicentric study reported an average tumor size of 7.3 cm for GBCCs and found a positive correlation between tumor size and metastatic potential [5].

According to the TNM classification, GBCCs are typically classified as T3 BCC and are categorized as high-risk BCCs under the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. While BCCs generally have a low metastatic potential, GBCCs, especially those exceeding 10 cm, are at increased risk of metastasis [6]. The National Comprehensive Cancer Network also evaluates basal cell carcinomas through their risk of relapse, so lesions larger than 20 cm on the trunk are considered high-risk for recurrence [2]. GBCCs are characterized by a higher incidence of tumor cell atypia and pleomorphism, approximately three times greater than that of conventional BCCs, further increasing the risk of local invasion and metastases [8].

Management of GBCC prioritizes wide local excision with histologically clear margins, often requiring reconstructive techniques. For advanced cases involving metastatic spread, adjuvant therapies such as chemoradiotherapy and hedgehog pathway inhibitors

are necessary [9, 10]. Systematic therapies may also reduce the incidence of local invasion, metastases, and recurrence [7]. However, most studies examining risk factors for local recurrence and the role of postoperative radiotherapy focus on BCCs of the head and neck. The treatment of BCCs on the trunk and extremities warrants further investigation [11]. In the present case, the delayed diagnosis highlights the critical importance of early detection and adherence to treatment protocols in preventing poor outcomes.

The primary factors influencing the size of GBCCs at the time of presentation appear to be patient neglect resulting in delayed diagnosis, as well as heightened biological aggressiveness, the cause of which is yet to be determined [12]. In at least 30% of cases, the primary factor contributing to the development of GBCC is neglect causing a delay in seeking medical attention, which averages around 7.5 ± 3.1 years. This delay is often linked to various factors, including poor socioeconomic conditions, inadequate hygiene, mental health issues, advanced age, and the painless nature of BCC lesions [13].

## Conclusion

Further research into the diagnosis and treatment of giant basal cell carcinoma is essential. Although only 1% of basal cell carcinomas progress to giant basal cell carcinoma, early detection by physicians or patients can effectively prevent excessive tumor growth and reduce the risk of metastasis, thereby improving outcomes for this rare condition. Early detection is vital in saving the lives of patients with basal cell carcinoma. Education of the general population plays a pivotal role in raising awareness about skin tumors, which are often painless and asymptomatic but can have fatal consequences if neglected. Educating individuals about the importance of regular skin self-examinations and timely medical; intervention is crucial for preventing adverse outcomes.

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# USING LOW DOSES OF DEXMEDETOMIDINE FOR PROCEDURAL SEDATION DURING MRI DIAGNOSTICS IN CHILDREN – CASE REPORT

# *PRIMENA NISKIH DOZA DEKSMEDETOMIDINA ZA SPROVOĐENJE PROCEDURALNE SEDACIJE TOKOM MRI DIJAGNOSTIKE KOD DECE – PRIKAZ SLUČAJA*

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**Abstract**

**Introduction.** Dexmedetomidine is a potent and highly selective $\alpha_2$-adrenergic agonist. Its sedative effects are mediated through the inhibition of neuronal activity in the locus coeruleus, which is rich in $\alpha_{2A}$-adrenergic receptors. In pediatric patients, sedation or general anesthesia is often required for certain diagnostic procedures, such as magnetic resonance imaging, due to limited cooperation in children under six years of age and the intense noise during scanning, ensuring patient tolerance and procedural success. **Case Report.** We present the case of a five-year-old boy referred for magnetic resonance imaging due to headaches and dizziness. Premedication was administered intramuscularly 30 minutes before the procedure, consisting of atropine (0.0125 mg/kg) and midazolam (0.1 mg/kg). Simultaneously, an initial intravenous bolus of dexmedetomidine (2 μg/kg) was infused over 15 minutes. The child was then transferred to the magnetic resonance imaging room, where sedation was maintained with a continuous intravenous infusion of dexmedetomidine at 0.25 μg/kg/h via an infusion pump, without additional anesthetic agents or bolus doses. No adverse effects, including bradycardia, respiratory disturbances, or desaturation were observed. **Conclusion.** Despite the use of a subminimal continuous dexmedetomidine dose compared to recommended dosing regimens, an adequate depth of sedation was achieved, allowing for high-quality magnetic resonance imaging without complications.

**Key words:** Dexmedetomidine; Hypnotics and Sedatives; Magnetic Resonance Imaging; Diagnostic Imaging; Child

**Sažetak**

**Uvod.** Deksmedetomidin je potentan i visokoselektivan $\alpha_2$ adrenergički agonista. Sedativne efekte ispoljava inhibicijom aktivnosti neurona *locus coeruleus*, u kome se nalazi veliki broj adrenergičkih $\alpha_{2A}$ receptora. Za potrebe pojedinih dijagnostičkih procedura, poput magnetne rezonancije, u pedijatrijskoj populaciji neophodno je pregled sprovesti u sedaciji/opštoj anesteziji, s obzirom na ograničenu saradnju dece mlađe od šest godina, te prisutnu intenzivnu buku tokom snimanja, kako bi dete tolerisalo pregled. **Prikaz slučaja.** Dat je prikaz slučaja dečaka starosti pet godina, koji je na magnetnu rezonanciju upućen pod dijagnozom glavobolje i vrtoglavice. Detetu je ordinirana intramuskularna premedikacija: atropin u dozi od 0,0125 mg/kg i midazolam u dozi od 0,1 mg/kg 30 minuta pre početka sprovođenja pregleda, uz istovremenu primenu i 15-minutne inicijalne bolus doze deksmedetomidina intravenski od 2 μg/kg. Neposredno pre započinjanja pregleda, dečak je premešten u prostoriju za pregled magnetnom rezonancijom. Bez dodatne primene nekog od anestetika, kao i bez dodatnih bolus doza deksmedetomidina, započeta je primena deksmedetomidina kontinuirano intravenski u dozi od 0,25 μg/kg/h preko infuzione pumpe. Nisu zabeležena neželjena dejstva kao bradikardija, poremećaji disanja i desaturacija. **Zaključak.** Iako je primenjena subminimalna kontinuirana doza deksmedetomidina u odnosu na preporučene režime doziranja, postignuta je odgovarajuća dubina sedacije i adekvatan kvalitet slika magnetne rezonancije.

**Ključne reči:** deksmedetomidin; hipnotici i sedativi; magnetna rezonanca; dijagnostički imidžing; dete

## Introduction

Dexmedetomidine is a potent and highly selective $\alpha_2$-adrenergic agonist [1], exerting dose-dependent sympatholysis, anxiolysis, sedation, hypnosis, and mild analgesia with minimal impact on respiratory function [2, 3]. Its sedative effects result from neuronal inhibition in the locus coeruleus, which is rich in $\alpha_{2A}$-adrenergic receptors. Dexmedetomidine also affects the cardiovascular system, with lower doses inducing bradycardia and hypotension, while higher doses may cause more pronounced bradycardia and hypertension. Due to these properties, $\alpha_2$-adrenergic agonists are widely used for sedation in both diagnostic procedures and intensive care units [4]. In pediatric patients, sedation or general anesthesia is often required for magnetic resonance imaging (MRI) due to limited cooperation, particularly in children

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***Abbreviations***

MRI – magnetic resonance imaging
CT – computed tomography
MAP – medial arterial pressure

under six years of age, and the intense noise generated during scanning. Adequate sedation ensures patient tolerate while maintaining high-quality imaging [5]. A recent meta-analysis reported an average dexmedetomidine induction dose of 2.8 ± 0.5 μg/kg (administered over 10 minutes) and the maintenance dose of 1.8 ± 0.4 μg/kg/h [6]. Here, we present a case from our clinical practice in which an MRI examination was successfully performed using dexmedetomidine at lower-than-standard doses.

## Case Report

A five-year old boy weighing 16 kg was referred for MRI due to headaches and dizziness. His mother reported a one-month history of headaches and four episodes of balance loss. A computed tomography (CT) scan performed in September 2023 suggests the presence of an anterior parasagittal right subarachnoid cyst, measuring 6x2x3 cm and chronic pansinusitis. The child was fully vaccinated for his age, with no history of chronic illnesses, allergies, or previous hospitalizations. On examination, congestion of the left nostril and slight pharyngeal hyperemia were noted. An otorhinolaryngology assessment revealed dried nasal secretions, mild pharyngeal hyperemia, and poor tympanic membrane transparency. Romberg's and Unterberger's tests were negative, and laboratory results were within normal limits.

Per institutional protocol, the mother was instructed to withhold oral intake from midnight, and intravenous Hartmann's solution (50 ml/h) was initiated to optimize cardiovascular volume.

On the day of the MRI, the child was alert and cooperative in the premedication room. He received intramuscular atropine (0.2 mg; 0.0125 mg/kg) and midazolam (1.5 mg; 0.1 mg/kg) 30 minutes before the procedure. Simultaneously, a 15-minute intravenous initial bolus of dexmedetomidine (2 μg/kg, total 32 μg) was administered, inducing sleep within minutes. Just before the MRI, the child was transported with minimal stimulation to the scanning room, remaining asleep throughout. Without additional anesthetic agents or bolus doses, a continuous intravenously infusion of dexmedetomidine (0.25 μg/kg/h) was initiated via an infusion pump. Headphones were placed over his ears to reduce noise exposure and prevent potential hearing damage. Hartmann's solution was infused at 130 ml/h, and the child breathed spontaneously with 100% oxygen (4 l/min) via a face mask. A pulse oximeter was used for monitoring, with blood pressure measurement omitted to minimize stimulation. The child's initial heart rate was 124 bpm, with transcutaneous oxygen saturation at 100%. No adverse effects, such as bradycardia, respiratory disturbances, or desaturation, were observed. Throughout the 45-minute MRI examination, the heart rate remained stable, with the final recorded value at 109 bpm, and saturation maintained at 100%. The total administered dexmedetomidine dose was 2.6 μg, with 100 ml of Hartmann's solution. The child remained adequately sedated, with no unwanted movements or awakening during the procedure. Upon completion, he woke up within minutes without complications.

## Discussion

Procedural sedation is increasingly utilized in the pediatric population [7]. Due to ongoing synaptogenesis and central nervous system development, children are particularly sensitive to anesthetics and sedatives, necessitating careful dose selection [8].The ideal sedative should have a rapid and predictable onset, a short half-life, dose-dependent effects, rapid action cessation, spontaneous breathing preservation, hemodynamic stability, painless administration, and a reversible action [9]. Successful MRI sedation depends on two key factors: procedural safety (low incidence of adverse events) and sedation effectiveness (successful completion of MRI) [10].

Dexmedetomidine is well-suited for MRI sedation, either alone or in combination with other anesthetics such as midazolam and propofol. Heard et al. [11] compared dexmedetomidine monotherapy (1 μg/kg bolus followed by 0.5 μg/kg/h infusion) with a combination of dexmedetomidine and midazolam (0.1 mg/kg). The dexmedetomidine-only group exhibited a shorter recovery time. Similarly, Koroglu et al. [12] compared dexmedetomidine (1 μg/kg bolus, 0.5 μg/kg/h infusion) to propofol (3 mg/kg bolus, 100 μg/kg/min infusion). Although propofol led to more frequent hypotension and desaturation, it also provided faster onset and recovery. Propofol, was associated with higher heart rate values but lower medial arterial pressure (MAP) and respiratory rates compared to dexmedetomidine, though these differences lacked clinical significance. Dexmedetomidine is characterized by prolonged recovery time [13]. Ahmed et al. [14] administered an initial 2 μg/kg dexmedetomidine bolus over 10 minutes, followed by 1 μg/kg/h dexmedetomidine infusion. If sedation was inadequate, an additional 2 μg/kg bolus was given. Bradycardia was

observed in 4.5% of cases, primarily in children aged 1– 3 years.

Although some studies suggest that lower dexmedetomidine doses (0.1-0.7 μg/kg/h) can achieve sedation, higher doses are generally recommended for MRI procedures to ensure procedural success [15, 16]. Recent findings support that the use of higher dexmedetomidine doses for MRI sedation, demonstrating good tolerability [17]. A retrospective study [18] administered a dexmedetomidine in an initial bolus dose of 2 μg/kg over 10 minutes, followed by a continuous 2 μg/kg/h infusion. If sedation was inadequate, an additional 2 μg/kg bolus was given, with midazolam or fentanyl added if necessary. This approach achieved successful sedation in 99.8% of cases - 78.5% with dexmedetomidine alone and 21.5% with adjunctive medications. No significant respiratory depression was observed, although apnea occurred in 0.1% of cases. A revised protocol by Ahmed et al. [14], increased the initial 10-minute loading dose of dexmedetomidine from 2 to 3 μg/kg and the continuous infusion from 1 to 1.5-2 μg/kg/h. raising the sedation from 91.8% to 97.6%. The Boston Sedation Protocol recommends a 3 μg/kg dexmedetomidine bolus over 10 minutes, followed by a 2 μg/kg/h infusion [19]. Liaudanskytė et al. [20] reported a 94.3% sedation success rate using a protocol with intravenous midazolam (0.15 mg/kg), a 3 μg/kg dexmedetomidine bolus over 10 minutes, and a continuous 2 μg/kg dexmedetomidine infusion. In the remaining 5.7% of cases, additional boluses of dexmedetomidine, midazolam, propofol or fentanyl were required.

In our experience, adequate MRI sedation is typically achieved with a 1.5-2 μg/kg dexmedetomidine bolus over 15 minutes, with or without intramuscular atropine and midazolam, followed by a 1.5-2 μg/kg/h infusion. When deeper sedation is required, additional dexmedetomidine and propofol boluses are preferred. This dosage regimen aligns with most published protocols. However, to our knowledge, the present case report is the first to document successful MRI sedation with a significantly lower continuous infusion of dexmedetomidine. The sedation was achieved with an initial 2 μg/kg bolus of dexmedetomidine, supplemented with intramuscular atropine and midazolam, followed by continuous administration of 0.25 μg/kg/h of dexmedetomidine.

## Conclusion

This case demonstrated that magnetic resonance imaging sedation can be effectively achieved with subminimal dexmedetomidine infusion (0.25 μg/kg/h), without adverse effects and while maintaining image quality. Potential factors contributing to this successful outcome include additional applied premedication, patient-specific physiological characteristics, and an individual response to the medication.

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# ACUTE CAROTID ARTERY OCCLUSION CAUSED BY TUMOR EMBOLI – CASE REPORT

# *AKUTNA OKLUZIJA KAROTIDNE ARTERIJE IZAZVANA TUMORSKIM EMBOLUSIMA – PRIKAZ SLUČAJA*

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**Abstract**

**Introduction.** Tumor embolism is a recognized but uncommon cause of cancer-related stroke. Unlike systemic emboli from left atrial myxomas, tumor emboli large enough to cause symptomatic cerebral ischemia are rare. Lung carcinoma may lead to embolization through spontaneous vascular invasion or secondary to surgical manipulation, with the latter being more frequent. **Case Report.** We present a 60-year-old woman with a history of lung adenocarcinoma but no active metastatic disease, who was admitted to our Clinic with acute right middle cerebral artery syndrome. On admission, a head computed tomography scan showed an Alberta Stroke Program Early Computed Tomography score of 8 in the right hemisphere. A computed tomography angiogram of the head and neck revealed occlusion of the right internal carotid artery, prompting administration of intravenous tissue plasminogen activator. The following day, a routine carotid ultrasound detected an atypical heterogeneous mass on the posterior wall of the right internal carotid artery, suggestive of a metastatic embolus with distal occlusion. Further evaluation with a contrast-enhanced chest computed tomography confirmed regional metastatic dissemination, showing adenocarcinoma progression to the superior mediastinum with satellite metastatic lesions. **Conclusion.** This case highlights spontaneous internal carotid artery occlusion due to tumor embolus spreading from lung cancer, leading to ischemic stroke. Our findings suggest that carotid ultrasound may be superior to computed tomography angiography in identifying tumor emboli, which could influence therapeutic decision-making in similar cases.

**Key words:** Carotid Arteries; Arterial Occlusive Diseases; Lung Neoplasms; Neoplasm Metastasis; Embolism; Ultrasonography, Carotid Arteries; Stroke

**Sažetak**

**Uvod.** Tumorska embolija je dobro prepoznata kao mogući mehanizam moždanog udara povezanog sa karcinomom. Isključujući sistemske tumorske embolije uzrokovane miksomima leve pretkomore, tumorski embolusi – dovoljno veliki da izazovu simptomatsku cerebralnu ishemiju, prilično su retki. Karcinom pluća može formirati embolus nakon invazije krvnih sudova spontano ili kao posledica hirurške manipulacije, što je češće. **Prikaz slučaja.** Predstavljamo slučaj 60-godišnje žene sa istorijom adenokarcinoma pluća, bez poznate dijagnoze aktivne metastatske bolesti, koja se javila u našu kliniku sa akutnim sindromom srednje moždane arterije desne strane. Na dan prijema, snimak kompjuterske tomografije glave pokazao je *Alberta Stroke Program Early Computed Tomography* skor osam u desnoj hemisferi, dok je kompjuterska angiografija glave i vrata pokazala okluziju desne unutrašnje karotidne arterije, nakon čega je pacijentkinja primila intravenski tkivni aktivator plazminogena. Sledećeg dana, rutinski ultrazvuk karotida pokazao je atipičnu heterogenu masu na zadnjem zidu desne unutrašnje karotidne arterije, nalik verovatnom metastatskom embolusu, sa distalnom okluzijom. De novo regionalna metastatska diseminacija potvrđena je kontrastnom kompjuterskom tomografijom grudnog koša, koji je pokazao progresiju adenokarcinoma na gornji medijastinum, sa satelitskim metastatskim lezijama. **Zaključak.** Ishemijski moždani udar kod naše pacijentkinje nastao je kao posledica spontane okluzije unutrašnje karotidne arterije tumorskim embolusom koji se proširio iz karcinoma pluća. Ovaj slučaj može ukazati na to da u sličnim situacijama ne treba zanemariti ultrazvuk karotida, jer može biti superiorniji od kompjuterske angiografije i shodno tome dovesti do drugačijih terapijskih odluka.

**Ključne reči:** karotidne arterije; arterijska okluzivna bolest; tumori pluća; metastaza; embolizam; ultrasonografija karotidnih arterija; moždani udar

## Introduction

Cancer-associated stroke (CAS) is a severe complication of malignancy, with an increased risk of ischemic stroke observed in the early stages of cancer diagnosis [1]. Patients with lung cancer have a 1.5-folds higher stroke risk compared to the general population [2]. The underlying mechanisms remain inconclusive but may include direct tumor effects, hypercoagulability, tumor embolism, or treatment-related factors such as chemotherapy [3]. Among these, tumor embolism often manifests as acute stroke due to cerebral artery occlusion [4]. Here, we present a case of acute stroke secondary to tumor embolism from lung adenocarcinoma.

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***Abbreviations***

CAS – cancer-associated stroke
MRI – magnetic resonance imaging
MRA – magnetic resonance angiography
CT – computed tomography
CTA – computed tomography angiography
ICA – internal carotid artery
ECA – external carotid artery
ASPECT – Alberta Stroke Program Early CT
IVT – intravenous thrombolysis
CCA – common carotid artery

**Case Report**

A 60-year-old woman was admitted to the Emergency Centre due to the sudden onset of left-side limb weakness 90 minutes before arrival. She had been diagnosed with lung adenocarcinoma two months prior, presenting as 78 x 89 x 74 mm tumor in the left upper lung lobe, infiltrating the aortic arch and left subclavian artery. A brain MRI and MR angiography (MRA) performed the day before admission showed no signs of metastasis, acute stroke, or atherosclerosis. She had received two cycles of chemotherapy, the last one a month prior.

Neurological examination revealed left central facial palsy, dysarthria, and left hemiparesis, with NIHSS score of 11. Initial brain CT and CT angiography (CTA) showed intraluminal thrombus in the right carotid bifurcation, no visible contrast in the orifice of the internal carotid artery (ICA) and external carotid artery (ECA), with Alberta Stroke Program Early CT (ASPECT) score of 8 **(Figure 1B).** Intravenous thrombolysis (IVT) was administered within three hours of symptom onset, but thrombectomy was not performed. A follow-up brain CT scan after 24 hours confirmed an acute infarction in the right hemisphere **(Figure 1A**).

On Day 2, a carotid ultrasound showed occlusion of the distal part of the right common carotid artery (CCA), bifurcation, ICA, and ECA with elongated,

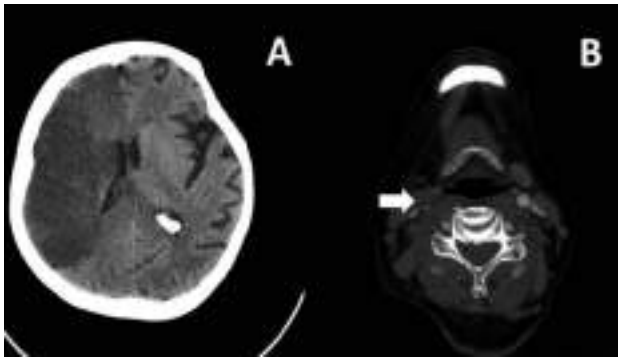


**Figure 1A, 1B.** Brain CT scan showing infarction in the right middle cerebral artery territory (1A); CT angiography showing right common carotid artery occlusion (1B)

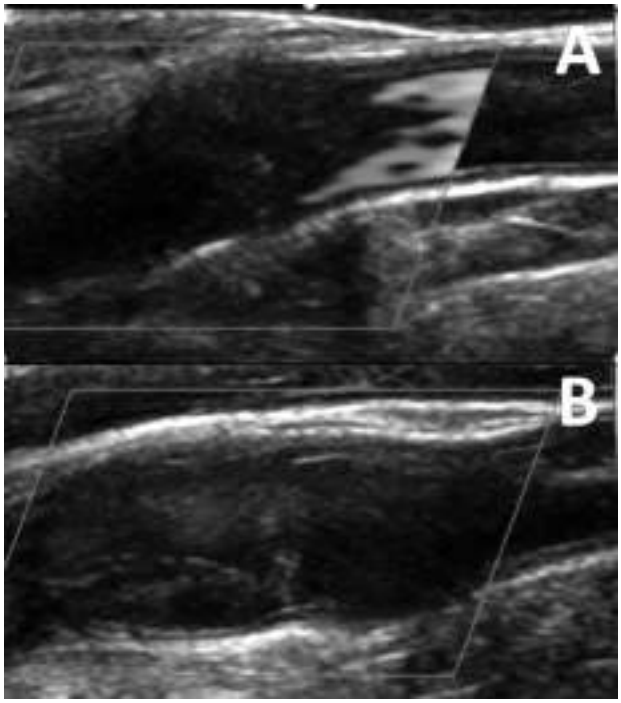


**Figure 2A, 2B.** B-mode carotid PW Doppler (longitudinal) showing occlusion in the distal right common carotid artery (2A); bifurcation and internal carotid artery with a hypoechoic mobile structure (2B)

mobile hypoechoic structures with irregular contours, moving with the cardiac cycle (**Figure 2A, 2B**).

An abdominal ultrasound showed no abnormalities, but a contrast chest CT scan confirmed progression of adenocarcinoma into the superior mediastinum with satellite metastatic lesions (**Figure 3A, 3B**).

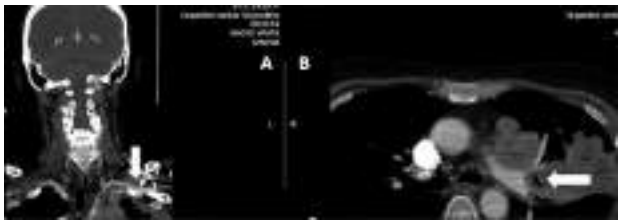


**Figure 3A, 3B.** Contrast-enhanced chest CT showing adenocarcinoma progression into the superior mediastinum with satellite metastatic lesions

Infiltration was also registered in over two-thirds of the aortic circumference, as well as the left subclavian artery and vein, with complete encasement of the left pulmonary artery. The patient received combined anticoagulant-antiplatelet therapy. On Day 17, she was referred to a physiotherapy center due to persistent neurological deficits, with an NIHSS score of 15.

## Discussion

Tumor emboli large enough to cause symptomatic cerebral ischemia are rare, except for systemic emboli from left atrial myxomas. Most cases originate from primary lung cancer, as seen in our patient [4]. Lung carcinoma may form an embolus after invading blood vessels via two mechanisms: spontaneous embolization due to direct tumor invasion into the bloodstream, and secondary to surgical manipulation, which is more common. In cancer-associated stroke (CAS), embolization typically occurs when tumor fragments enter the circulation, leading to stroke. The distal internal carotid artery (ICA), middle cerebral arteries, basilar artery, and lacunar arteries are the most frequently affected [1, 4]. However, definitive diagnosis requires histological confirmation from an embolus specimen or post-mortem analysis [4].

Carotid ultrasound is essential for detecting mobile plaques, which are associated with recurrent stroke [5]. The most common etiology is complicated atherosclerotic plaque, which is non-atherosclerotic in malignancy, pregnancy, inflammatory, and infectious states [2, 6]. The mobile plaques are classified based on ultrasound morphology as follows: 1) jellyfish type - a part of the fibrous cap is mobile; 2) streaming-band type - a part of the ruptured fibrous cap is fluttering; 3) mobile thrombus type - a tethered thrombus caused by plaque rupture is mobile, and 4) fluctuating ulcer type - a part of the ulcer is pulsating [5].

In our case, carotid ultrasound revealed a hypoechoic mobile structure, distinct from typical carotid atherosclerotic plaques. The mobile structure resembled the jellyfish type but lacked a fibrous cap. Given the absence of vascular risk factors, CCA intima thickening, and conventional plaque morphology, a tumor embolus was suspected. Although CTA is highly-effective for evaluating luminal stenosis, it cannot visualize mobile plaques, making carotid ultrasound the superior modality in such cases [7].

The optimal treatment for CAS remains undefined, there is limited evidence supporting IVT efficacy, except in case reports involving atrial myxoma [8, 9]. In theory, IVT is unlikely to recanalize a vessel occluded by a tumor embolus, as observed in our patient [10]. However, AHA/ASA guidelines do not exclude CAS patients from IVT [11]. According to the author's opinion, embolectomy may have been a more effective therapeutic option, as suggested by previous reports [4].

## Conclusion

Cancer is often underestimated as a stroke risk factor, particularly in cases of tumor embolism. Carotid ultrasound is the only real-time imaging modality capable of detecting mobile carotid lesions, unlike static angiographic methods such as computed tomography angiography. The optimal treatment strategy for cancer-associated stroke remains uncertain, but thrombolytic therapy should not be withheld, even though embolectomy may offer better outcomes.

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# IMPORTANCE OF ULTRASOUND IN SCREENING DENSE BREASTS – CASE REPORT

# *ZNAČAJ ULTRAZVUČNOG PREGLEDA U SKRININGU DOJKI GUSTOG TKIVA – PRIKAZ SLUČAJA*

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Case report
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**Abstract**

**Introduction.** Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related mortality in women. While mammography remains the only screening method proven to reduce breast cancer mortality, its sensitivity is significantly lower in women with dense breast tissue, ranging from 30% to 48%. Supplementary ultrasound screening is effective in detecting mammographically occult cancers in these women. **Case Report.** A 40-year-old female presented for a baseline mammogram, which revealed very dense breast tissue but no pathological changes. However, a cluster of altered lymph nodes was detected in the right axilla. Subsequent ultrasound examination identified speculated soft tissue changes in the retroareolar region of the right breast, as along with pathologically altered lymph nodes in the right axilla. The findings were classified as Breast Imaging-Reporting and Data System 5 l.dex, prompting a CORE biopsy. Pathohistological analysis confirmed breast cancer (Estrogen Receptor 0, Progesterone Receptor 0, Human Epidermal growth factor Receptor 2 3+, Ki-67 Antigen 31%) with axillary metastasis (Estrogen Receptor 0, Progesterone Receptor 0, Human Epidermal growth factor Receptor 2 3+, Ki-67 Antigen 15%). **Conclusion.** Mammography remains the gold standard for breast cancer screening tool but has reduced sensitivity in women with dense breast tissue compared to women with fatty replaced tissue. This case underscores the importance of supplemental ultrasound in detecting mammographically occult breast cancer.

**Key words**: Fibrocystic Breast Disease; Ultrasonography; Mammography; Breast Neoplasms

**Sažetak**

**Uvod.** Karcinom dojke je najčešće dijagnostikovani malignitet i vodeći uzrok smrti od karcinoma kod žena. Mamografija je jedini metod za skrining koji je dokazano povezan sa smanjenjem smrtnosti od karcinoma dojke. Osetljivost mamografije varira i kreće se od 30% do 48% kod žena sa gustim tkivom dojki. Ultrazvuk za skrining je efikasan u otkrivanju mamografski skrivenog karcinoma kod žena sa gustim tkivom. **Prikaz slučaja.** Pacijentkinja starosti 40 godina, dolazi na prvu mamografiju. Na baznom mamogramu vrlo gustih dojki nisu uočene patološke promene u obe dojke. Međutim, u desnoj aksili je uočen konglomerat izmenjenih limfonodusa. Na ultrazvučnom pregledu desne dojke retroareolarno uočene je spikulirana mekotkivna promena, kao i patološki izmenjeni limfni čvorovi u desnoj aksili. Ultrazvučni nalaz desne dojke klasifikovan je kao *Breast Imaging-Reporting and Data System 5*, što ukazuje na visok stepen sumnje na malignitet. Pacijentkinja je podvrgnuta CORE biopsiji, a patohistološki nalaz je pokazao karcinom dojke, sa receptorom estrogena 0, receptorom progesterona 0, receptorom humanog epidermalnog faktora rasta 2 3+, Ki-67 antigen (protein povezan sa proliferacijom ćelija) 31%. Biopsija aksilarnog limfnog čvora takođe je pokazala slične nalaze sa receptorom estrogena 0, receptorom progesterona 0, receptorom humanog epidermalnog faktora rasta 2 3+, Ki-67 antigen (protein povezan sa proliferacijom ćelija) 15%. **Zaključak.** Mamografija je trenutno jedini alat za skrining karcinoma dojke koji je dokazano povezan sa smanjenjem smrtnosti od karcinoma. Međutim, mamografija je manje efikasna u otkrivanju karcinoma kod žena sa gustim tkivom dojki u poređenju sa ženama sa masnim tkivom dojke. Ovaj prikaz slučaja pokazuje značaj dodatnog ultrazvučnog pregleda kod pacijentkinja sa gustim tkivom dojki.

**Ključne reči:** dojke gustog tkiva; ultrasonografija; mamografija; tumori dojke

## Introduction

Breast cancer is the most frequently diagnosed cancer and is the leading cause of cancer related death in women. The global burden of breast cancer continues to rise, with an estimated 2.3 million new cases diagnosed annually [1]. Early detection through screening is crucial for improving survival outcomes, with studies showing that annual screening beginning at age 40 can reduce breast cancer mortality by up to 40% [2]. Mammography has long been the gold standard for breast cancer screening, and its association with reduced breast cancer mortality has been well established [3]. However, the sensitivity of mammography is variable, ranging from 80% to 98% in women with fatty breast tissue to as low as 30% to

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***Abbreviations***

BI-RADS– Breast Imaging-Reporting and Data System
ER – Estrogen Receptor
PR – Progesterone Receptor
HER2 – Human Epidermal growth factor Receptor 2
Ki67 – Ki-67 Antigen (protein related to cell proliferation)

48% in women with dense breast tissue [4]. Dense breast tissue can obscure tumors on mammograms, which increases the likelihood of false negatives and delayed diagnoses [5].

In response to these challenges, ultrasound has emerged as a valuable adjunct to mammography in women with dense breast tissue. Recent studies have shown that screening ultrasound can detect cancers that may be missed on mammograms, particularly in women with high breast density [6]. A study by Glechner et al. [7] demonstrated that adding ultrasound to mammography significantly improved the detection rate of breast cancers in dense-breast women, with a reduction in the number of false negatives. Despite the added benefits, ultrasound screening is not without limitations, breast US has been criticized for increasing the number of false-positive findings [8]. Nonetheless, recent evidence supports the use of supplemental ultrasound screening as an effective means of improving breast cancer detection in women with dense breasts [9]. This case report explores

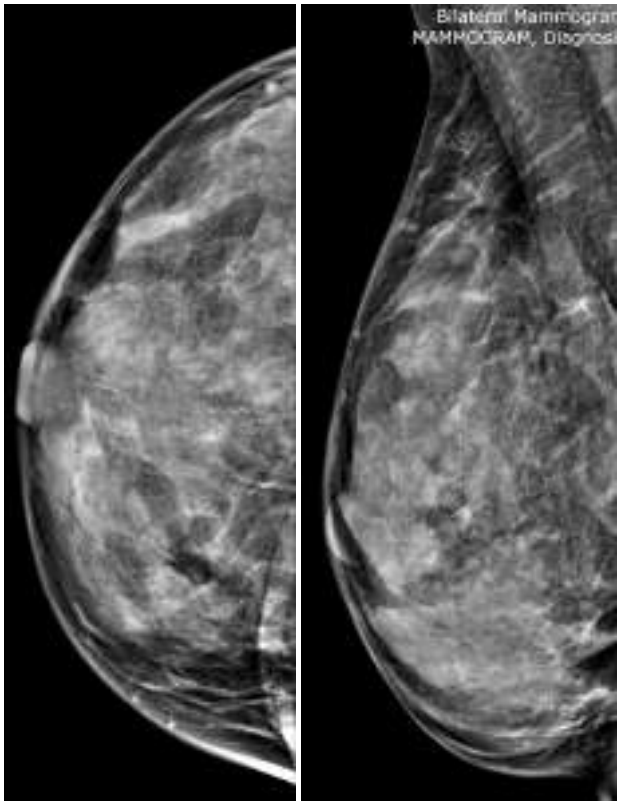

**Figure 1.** Mammography of the right breast in CC and MLO projection – BI RADS 2

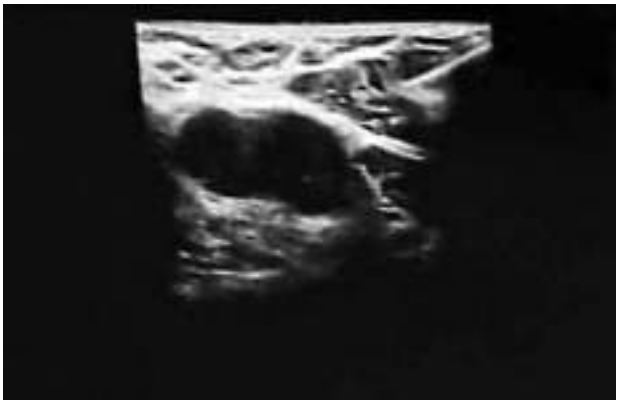

**Figure 2.** Ultrasound of the right axilla

the challenges of breast cancer detection in women with dense breast tissue and emphasizes the role of ultrasound in enhancing early diagnosis [10].

**Case report**

A 40-year-old woman presented for her first baseline mammogram. A previous ultrasound examination had been classified as Breast Imaging-Reporting and Data 2 (BI-RADS 2), indicating no pathological findings. The patient had no significant family history of breast cancer, suggesting a low-risk profile.

The baseline mammogram revealed extremely dense breast tissue (BI-RADS 2), with no visible pathological changes **(Figure 1).** However, a clustered of altered lymph nodes was detected in the right axilla, prompting further evaluation.

A supplementary ultrasound was performed, revealing spiculated soft tissue changes in the retroareolar region of the right breast, measuring approximately 23 x 22 mm **(Figure 2),** and pathologically altered axillary lymph nodes **(Figure 3).** Based on these findings, the classification was upgraded to BI-RADS 5 l.dex, indicating a high suspicion of malignancy.

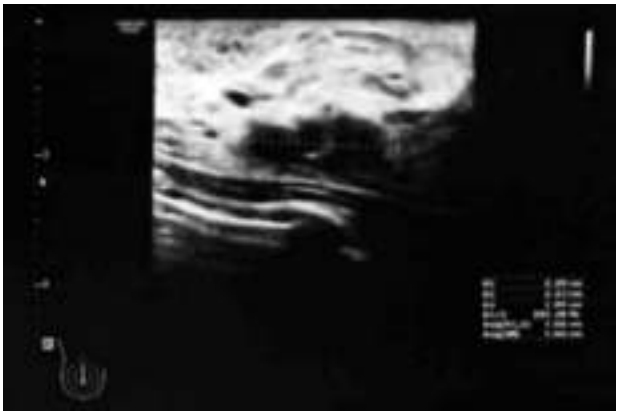

**Figure 3.** Ultrasound of the right breast – BI RADS 5

The CORE needle biopsy HER2-positive invasive breast cancer with the following markers: Estrogen Receptor (ER)-negative (0), Progesterone Receptor (PR)-negative (0), Human Epidermal growth factor Receptor 2 (HER2)-positive (3+), and Ki-67 Antigen (protein related to cell proliferation) (Ki67) index of 31%. Furthermore, the pathological evaluation of the axillary lymph nodes revealed a similar profile: ER-negative (0), PR-negative (0), HER2-positive (3+), with a Ki67 index of 15%.

The patient is currently undergoing neoadjuvant chemotherapy with the Adriamycin-Cyclophosphamide protocol, with follow-up and additional treatment plans based on the therapeutic response.

## Conclusion

Mammography remains the primary screening tool for breast cancer, but its effectiveness is significantly reduced in women with dense breast tissue, increasing the risk of missed diagnoses. This case report highlights the importance of supplemental ultrasound, demonstrating its ability to detect mammographically occult breast cancer. Integrating ultrasound into routine screening for women with dense breasts could enhance cancer detection, improve diagnostic accuracy, and facilitate early intervention - ultimately leading to better patient outcomes.

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# BOOK REVIEWS
# *PRIKAZI KNJIGA*

**Dobanovački D, Slavković A, Vučković N. Neonatal Urology** (Urologija novorođenčeta i malog deteta). Novi Sad 2024. **Front cover** designed by Vojnov Tanja, Dobanovački Dušanka. **Printed** by Mala knjiga Novi Sad 2024, first edition, non-commercial distribution. **Cataloguing and publication data**: Library of Matica srpska, Novi Sad, Serbia, UDK 616.6-053.2; ISBN 978-86-903028-2-6; COBISS.SR-ID 149884425


Pediatric urology emerged as a result of experience of specialists addressing surgical challenges in urology and pediatrics. Understanding the embryology of the urogenital tract anomalies, development of diagnostic techniques and surgical innovations over recent decades have steered pediatric urologists to focus on prenatal and early postnatal life.

The text offered to readers has ten chapters. The first chapter specifies the clinical anatomy and embryology of the urogenital tract, detailing the development of common congenital anomalies. Chapter two presents contemporary perspectives on multicystic kidney, one of the most intriguing renal anomalies. Chapter three provides an in-depth morphological-functional analysis of congenital anomalies in the urinary tract's collector system, including obstructive and reflux-related anomalies observed step-by-step both prenatally and postnatally. Decades of collaborative efforts in early anomaly detection and timely surgical interventions is illustrated with characteristic case studies. Chapter four reviews the outcomes of surgical treatment for megaureter, offering comparative insights from the literature. Chapters five, six and seven address complex anomalies, such as prune-belly syndrome, exstrophic anomalies, and posterior urethral valves. Each chapter clearly outlines clinical presentations, diagnostic and therapeutic options. The eighth chapter presents problems in uro-oncology related to early-life malignancies like neuroblastoma, nephroblastoma, and rhabdomyosarcoma. It includes detailed tumor staging classifications alongside modern treatment methods and outcomes. Chapter nine of the manual includes challenges in emergencies, such as acute scrotum, adrenal hemorrhage, hymen atresia, prolapsed ureterocele, and incarcerated inguinal hernia, with a detailed list of symptoms, emergency diagnostic procedures, and emergency surgical management methods. Chapter ten is dedicated to diagnostic imaging techniques, supplemented by photo documentation with description. Part two of this chapter highlights endoscopic interventions in pediatric urology, including descriptions and experiences with neonatal and infant percutaneous nephrostomies, as well as guidelines for urethrocystoscopy and endoscopic treatment of vesicoureteral reflux, based on global expert recommendations.

A notable addition to the manual is a retrospective overview of the Department of Pediatric Urology at the Institute for Health Care of Children and Youth of Vojvodina in Novi Sad, chronicling its fifty-year history of dedication and innovation.

This manual is an eloquent and vivid presentation of many years of work and experience of experts dedicated to addressing urogenital challenges in early life stages. It is designed for young professionals embarking on careers, and features plenty practical advice and detailed presentations of interesting complex cases.

Approval for the use and publication of archive photo documentation was obtained from Ethics Committee of the Institute for Health Care of Children and Youth of Vojvodina in Novi Sad, and the Institute Director. Cataloged by *Matica srpska* in Novi Sad, the manual was printed in Serbian with color photos in a limited run of 150 copies. It has been distributed to medical residents in pediatric surgery, anesthesia, and pediatrics. Full text, and all the references that have been used, is available online at: https://www.izzzdiovns.rs/nastava-i-nauka/

As the manual's motto, *VADE MECUM* ("come with me"), suggests, its authors aim to guide the next generation of professionals with their shared knowledge and extensive experience.

*Prim. dr Predrag Ilić,*
Specialist pediatric surgeon and urologist,
reviewer of the manual
Institute for Mother and Child Health Care
«Dr Vukan Čupić» New Belgrade

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# INDEX KEY WORDS

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