# TIMOČKI MEDICINSKI GLASNIK

# TIMOK MEDICAL GAZETTE

**Glasilo zaječarske podružnice Srpskog lekarskog društva**
**The Bulletin of the Zajecar branch of the Serbian Medical Association**

**Izlazi od 1976.**
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# PROCENA DIJAGNOSTIČKE VREDNOSTI PREOPERATIVNIH LABORATORIJSKIH I RADIOLOŠKIH PARAMETARA U KLASIFIKACIJI TEŽINE AKUTNOG APENDICITISA

*Srđan Milina, Branko Lukić, Marija Nikolić, Nemanja Trifunović, Milica Radivojević, Dimitrije Surla*

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**SAŽETAK**: **Uvod:** Akutni apendicitis predstavlja najčešće intraabdominalno hitno hirurško stanje. Precizno razlikovanje između nekomplikovanog i komplikovanog apendicitisa od suštinskog je značaja za određivanje optimalne terapije i smanjenje postoperativnog morbiditeta. Iako laparoskopska apendektomija ostaje zlatni standard, konzervativno lečenje sve češće se razmatra kao adekvatna opcija kod nekomplikovanih slučajeva. **Cilj** naše studije bio je da istakne značaj preoperativne laboratorijske i radiološke dijagnostike u proceni težine intraoperativnih nalaza kod akutnog apendicitisa i optimizaciji terapijske strategije. **Metodologija:** Ova retrospektivna studija obuhvatila je 231 pacijenta sa dijagnozom akutnog apendicitisa, lečenih u Kliničko-bolničkom centru Zemun u periodu od decembra 2021. do septembra 2023. godine. Pacijenti su podeljeni u grupe sa nekomplikovanim i komplikovanim apendicitisom na osnovu kliničkih, intraoperativnih i histopatoloških nalaza. Demografski, klinički, laboratorijski i ultrazvučni podaci upoređeni su između grupa. Statistička obrada podataka izvršena je korišćenjem SPSS verzije 21. **Rezultati:** Komplikovani apendicitis dijagnostikovan je kod 63 pacijenta (27,27%), koji su bili značajno stariji i imali duže trajanje simptoma ($p<0,01$). Povišena telesna temperatura, leukocitoza i povišene vrednosti C-reaktivnog proteina (CRP) bili su češći u grupi sa komplikovanim apendicitisom. Prosečna koncentracija CRP-a bila je značajno viša u grupi sa komplikacijama (109 mg/L) u poređenju sa grupom bez komplikacija (24,55 mg/L, $p<0,01$). Ultrazvuk je pokazao limitiranu mogućnost razlikovanja težine bolesti. Nije utvrđena značajna povezanost između dijabetesa melitusa i kompleksnosti bolesti. **Zaključak:** Naša studija potvrđuje da su starije životno doba, povišena temperatura, produženo trajanje simptoma i povišen CRP značajni faktori povezani sa komplikovanim formama akutnog apendicitisa. CRP se izdvojio kao najpouzdaniji preoperativni biomarker za procenu težine bolesti. Ovi rezultati ističu značaj povezivanja kliničke procene sa odabranim laboratorijskim parametrima, posebno vrednostima CRP-a, u cilju unapređenja preoperativne dijagnostike i donošenja blagovremene i adekvatne terapijske odluke.
**Ključne reči:** akutni apendicitis, CRP, komplikovani apendicitis, dijagnoza, laboratorijski markeri

## UVOD

Akutni apendicitis je najčešće intraabdominalno hirurško hitno stanje [1]. U Srbiji je morbiditet akutnog apendicitisa sličan globalnim trendovima, a ukupan rizik oboljevanja tokom života iznosi približno 8,6 % kod muškaraca i 6,7 % kod žena [2]. Dijagnoza i lečenje akutnog apendicitisa mogu biti složeni, jer zahtevaju isključivanje različitih diferencijalnih dijagnoza i priorizaciju hirurške intervencije u skladu sa težinom bolesti. Pravovremeno i precizno lečenje ostaje ključno za smanjenje morbiditeta povezanog sa apendicitisom.

Razlikovanje nekomplikovanog i komplikovanog apendicitisa je od suštinskog značaja za određivanje odgovarajućeg terapijskog pristupa [3]. Neadekvatna ili odložena dijagnoza i lečenje komplikovanog apendicitisa povezani su sa ozbiljnim komplikacijama i postoperativnim morbiditetom, što dodatno naglašava važnost identifikovanja parametara koji odražavaju težinu bolesti [4].

Precizna diferencijacija između ova dva oblika ima za cilj podršku u izboru najadekvatnije terapije, uz istovremeno smanjenje broja nepotrebnih hirurških intervencija i rizika od pratećih komplikacija. Pored laparoskopske apendektomije, koja ostaje zlatni standard u lečenju komplikovanog apendicitisa, konzervativni pristup se sve češće


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# DIAGNOSTIC VALUE OF PREOPERATIVE LABORATORY AND IMAGING PARAMETERS IN STRATIFYING APPENDICITIS SEVERITY

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**ABSTRACT: Background:** Acute appendicitis is the most common intra-abdominal surgical emergency. Accurate differentiation between uncomplicated and complicated appendicitis is essential for determining optimal treatment and minimizing postoperative morbidity. While laparoscopic appendectomy remains the gold standard, conservative management is increasingly considered a viable option for uncomplicated cases. **The aim** of our study was to highlight the importance of preoperative laboratory and imaging diagnostics in differentiating the severity of intraoperative findings in acute appendicitis and optimizing therapeutic strategy. **Methods:** This retrospective study analyzed 231 patients diagnosed with acute appendicitis at the Clinical Hospital Center Zemun between December 2021 and September 2023. Patients were stratified into uncomplicated and complicated appendicitis groups based on clinical, intraoperative, and histopathological findings. Demographic, clinical, laboratory and ultrasonographic data were compared between groups. Statistical analyses were performed using SPSS version 21. **Results:** Complicated appendicitis was present in 63 patients (27.27%), who were significantly older and had longer symptom duration ($p < 0.01$). Febrile episodes, leukocytosis, and elevated CRP levels were more prevalent in the complicated group. The mean CRP concentration was significantly higher in the complicated group (109 mg/L) compared to the uncomplicated group (24.55 mg/L, $p < 0.01$). Ultrasonography showed limited ability to differentiate between disease severities. No significant association was found between diabetes mellitus and disease complexity. **Conclusion:** Our study confirms that older age, fever, prolonged symptom duration, and elevated CRP levels are key factors associated with complicated acute appendicitis. CRP stood out as the most reliable preoperative biomarker for assessing disease severity. These results emphasize the need to integrate clinical evaluation with selected laboratory markers, especially CRP to improve preoperative diagnosis and guide timely treatment.

**Keywords:** acute appendicitis, CRP, complicated appendicitis, diagnosis, laboratory markers

## INTRODUCTION

Acute appendicitis is the most common intra-abdominal surgical emergency [1]. In Serbia, the morbidity of acute appendicitis is similar to global trends, and the overall lifetime risk is approximately 8.6% in men and 6.7% in women [2]. The diagnosis and management of acute appendicitis can be complex, as they require the exclusion of various differential diagnoses and prioritization of surgical intervention according to disease severity. Timely and accurate treatment remains essential for reducing appendicitis-related morbidity.

Distinguishing between uncomplicated and complicated appendicitis is crucial for determining the appropriate therapeutic approach [3]. Inadequate or delayed diagnosis and treatment of complicated appendicitis are associated with serious complications and postoperative morbidity, further emphasizing the importance of identifying parameters that reflect disease severity [4].

Accurate differentiation between these two forms aims to support the selection of the most appropriate therapy, while simultaneously reducing the number of unnecessary surgical interventions and the risk of associated complications. In addition to laparoscopic appendectomy, which remains the gold standard for the treatment of complicated appendicitis, a conservative approach is increasingly being used in the management of uncomplicated cases [5–7].

The diagnosis of appendicitis is primarily based on the clinical presentation, although inflammatory markers, ultrasound, and

primenjuje u terapiji nekomplikovanih slučajeva [5–7].

Dijagnoza apendicitisa se prvenstveno postavlja na osnovu kliničke slike, iako markeri zapaljenja, ultrazvuk i kompjuterizovana tomografija mogu doprineti tačnosti dijagnoze [8]. U našoj ustanovi, ultrazvučni pregled se rutinski koristi zajedno sa određivanjem nivoa C-reaktivnog proteina (CRP) i broja leukocita (WBC) kako bi se olakšala dijagnoza i procenila težina bolesti. CT se koristi retko i to samo u slučajevima kada klinička slika i laboratorijski nalazi nisu dovoljno jasni. C-reaktivni protein (CRP) je upalni marker koji je u više studija identifikovan kao nezavisan prediktor komplikovanog apendicitisa. [9,10)

Glavni cilj ove studije jeste da se utvrdi da li se CRP može koristiti za razlikovanje komplikovanog (gangrenoznog ili perforiranog) i nekomplikovanog apendicitisa.

## MATERIJALI I METODE

Ova studija predstavlja retrospektivnu analizu 231 pacijenta sa kliničkim znacima akutnog apendicitisa, koji su bili hospitalizovani na Odeljenju opšte hirurgije Kliničko-bolničkog centra (KBC) Zemun u periodu od decembra 2021. do septembra 2023. godine. Svi podaci korišćeni u istraživanju preuzeti su iz medicinske dokumentacije. Pacijenti su podvrgnuti hirurškom lečenju, i to otvorenom ili laparoskopskom apendektomijom, a dijagnoza akutnog apendicitisa potvrđena je postoperativnim histopatološkim pregledom operisanog apendiksa.

Na osnovu kliničkih, intraoperativnih i histopatoloških nalaza, pacijenti su podeljeni u dve grupe: one sa nekomplikovanim apendicitisom i one sa komplikovanim apendicitisom. Nekomplikovani apendicitis definisan je kao kataralna ili flegmonozna upala apendiksa. S druge strane, komplikovani apendicitis se odnosi na gangrenoznu upalu, sa ili bez perforacije.

Pored analize i poređenja nivoa C-reaktivnog proteina, broja leukocita i ultrazvučnih nalaza, u studiji su ispitivani i različiti klinički i demografski parametri. Uključeni su: trajanje simptoma, prisustvo ili odsustvo febrilnih epizoda, kao i postojanje komorbiditeta. Takođe, osnovne demografske karakteristike kao što su pol i starost pacijenata uključene su u analizu u cilju procene njihovog potencijalnog uticaja na kliničku prezentaciju i tok bolesti. Telesna temperatura viša od 37,4°C smatrana je značajnom. Svaka sumnja na apendicitis na osnovu kliničkog pregleda dodatno je potvrđena obaveznim laboratorijskim analizama i ultrazvučnim pregledom kako bi se povećala dijagnostička tačnost i usmerilo dalje lečenje. Pozitivan ultrazvučni nalaz postavljan je na osnovu identifikacije jednog ili više od sledećih kriterijuma: prisustvo slobodne intraperitonealne tečnosti, regionalne limfadenopatije i/ili povećan dijametar apendiksa sa zadebljanjem zida apendiksa.

Statistička analiza sprovedena je korišćenjem softvera SPSS verzija 21. Varijable između dve grupe pacijenata poređene su Mann-Whitney U testom za numeričke podatke i hi-kvadrat testom za kategorijalne podatke. Statistička značajnost definisana je kao p-vrednost manja od 0,05.

## REZULTATI

Uzorak od 231 pacijenta dijagnostikovanih sa apendicitisom tokom perioda istraživanja podeljen je u dve grupe. Prvu grupu činilo je 168 pacijenata (72,73%) sa nekoplikovanim apendicitisom, dok je drugu grupu činilo 63 pacijenta (27,27%) sa komplikovanim apendicitisom. Ukupna populacija pacijenata obuhvatala je 110 muškaraca (47,62%) i 121 ženu (52,38%). Među pacijentima sa komplikovanim apendicitisom, 34 (54%) su bili muškarci, a 29 (46%) žene, dok je u grupi sa nekoplikovanim apendicitisom 76 (45,2%) bilo muškaraca, a 92 (54,8%) žena. Nije uočena statistički značajna razlika u distribuciji pola između dve grupe (p=0,242).

Naši pacijenti su imali prosečnu starost od 40,31 ± 17,06 godina, pri čemu je najmlađi pacijent imao 16, a najstariji 80 godina. U podgrupi pacijenata sa komplikovanim apendicitisom, medijana starosti iznosila je 47 godina. Nasuprot tome, pacijenti sa nekoplikovanim apendicitisom bili su značajno mlađi, sa medijanom starosti od 34 godine, što predstavlja statistički značajnu razliku (p<0,01).

computed tomography can contribute to diagnostic accuracy [8]. In our institution, ultrasound examination is routinely used together with the assessment of C-reactive protein (CRP) levels and white blood cell (WBC) count to facilitate diagnosis and evaluate disease severity. CT is used rarely, and only in cases where the clinical presentation and laboratory findings are not sufficiently clear. C-reactive protein (CRP) is an inflammatory marker that has been identified in several studies as an independent predictor of complicated appendicitis [9,10].

The main objective of this study is to determine whether CRP can be used to distinguish between complicated (gangrenous or perforated) and uncomplicated appendicitis.

## MATERIALS AND METHODS

This study presents a retrospective analysis of 231 patients with clinical signs of acute appendicitis who were hospitalized at the Department of General Surgery of the Clinical Hospital Center (KBC) Zemun between December 2021 and September 2023. All data used in the study were obtained from medical records. The patients underwent surgical treatment, either open or laparoscopic appendectomy, and the diagnosis of acute appendicitis was confirmed by postoperative histopathological examination of the removed appendix.

Based on clinical, intraoperative, and histopathological findings, the patients were divided into two groups: those with uncomplicated appendicitis and those with complicated appendicitis. Uncomplicated appendicitis was defined as catarrhal or phlegmonous inflammation of the appendix, whereas complicated appendicitis referred to gangrenous inflammation, with or without perforation.

In addition to analyzing and comparing C-reactive protein levels, white blood cell counts, and ultrasound findings, the study also assessed various clinical and demographic parameters. These included symptom duration, the presence or absence of febrile episodes, and the existence of comorbidities. Basic demographic characteristics such as patient sex and age were also included to evaluate their potential impact on clinical presentation and disease course. A body temperature higher than 37.4°C was considered significant.

Every clinical suspicion of appendicitis was further confirmed by mandatory laboratory analyses and ultrasound examination to increase diagnostic accuracy and guide further management. A positive ultrasound finding was established based on the identification of one or more of the following criteria: presence of free intraperitoneal fluid, regional lymphadenopathy, and/or an increased appendiceal diameter with thickening of the appendiceal wall.

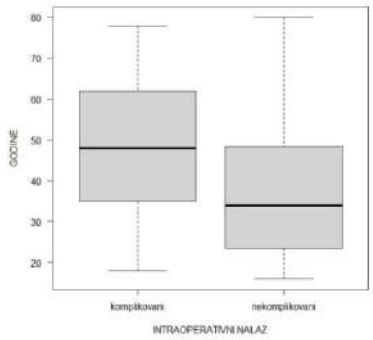
Statistical analysis was performed using SPSS software, version 21. Variables between the two patient groups were compared using the Mann–Whitney U test for numerical data and the chi-square test for categorical data. Statistical significance was defined as a p-value of less than 0.05..

## RESULTS

The sample of 231 patients diagnosed with appendicitis during the study period was divided into two groups. The first group consisted of 168 patients (72.73%) with uncomplicated appendicitis, while the second group included 63 patients (27.27%) with complicated appendicitis. The overall patient population comprised 110 men (47.62%) and 121 women (52.38%). Among patients with complicated appendicitis, 34 (54%) were men and 29 (46%) were women, whereas in the group with uncomplicated appendicitis, 76 (45.2%) were men and 92 (54.8%) were women. No statistically significant difference in sex distribution was observed between the two groups ($p = 0.242$).

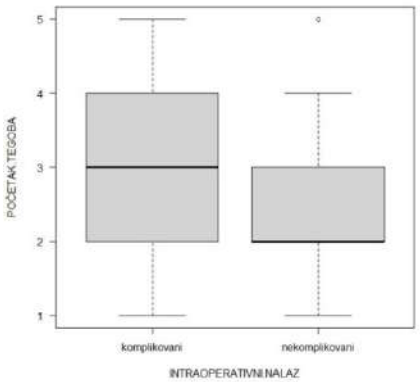
The mean age of our patients was 40.31 ± 17.06 years, with the youngest patient being 16 and the oldest 80 years old. In the subgroup of patients with complicated appendicitis, the median age was 47 years. In contrast, patients with uncomplicated appendicitis were significantly younger, with a median age of 34 years, representing a statistically significant difference ($p < 0.01$).

**Slika 1.** Box-plot dijagram prikazuje odnos između starosti pacijenata i intraoperativnih nalaza komplikovanog i nekomplikovanog apendicitisa. Dijagram ukazuje na statistički značajnu razliku u težini intraoperativnih nalaza između mlađih i starijih pacijenata. Središnja linija u svakom boksu predstavlja medijanu starosti, dok ivice boksa označavaju prvi i treći kvartil.




Kod većine pacijenata sa komplikovanim zapaljenjem simptomi su se javili u intervalu od 24 do 48 sati pre postavljanja preoperativne dijagnoze. S druge strane, pacijenti sa nekoplikovanim zapaljenjem najčešće su imali simptome kraće od 24 sata pre dolaska u bolnicu. Ova razlika u trajanju simptoma između dve grupe bila je statistički značajna ($p<0,01$), što ukazuje na povezanost dužeg trajanja simptoma sa razvojem komplikovane bolesti. Ovi nalazi naglašavaju važnost rane kliničke procene i intervencije u cilju smanjenja rizika od komplikacija.

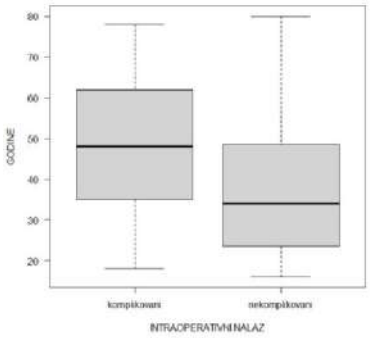
**Slika 2.** Box-plot dijagram prikazuje odnos između trajanja simptoma i intraoperativnih nalaza komplikovanog i nekomplikovanog apendicitisa. Dijagram pokazuje da je duže trajanje simptoma povezano sa većom učestalošću komplikovanih intraoperativnih nalaza. Središnja linija u svakom boksu predstavlja medijanu trajanja, dok ivice boksa označavaju prvi i treći kvartil.




Ukupno 63 pacijenta (27,27%) imala su epizode povišene telesne temperature tokom trajanja simptoma, od kojih je 26 bilo sa komplikovanim, a 37 sa nekoplikovanim apendicitisom. S obzirom na razliku u veličini grupa, razlika u prisustvu povišene telesne temperature između grupa bila je statistički značajna ($p<0,01$).

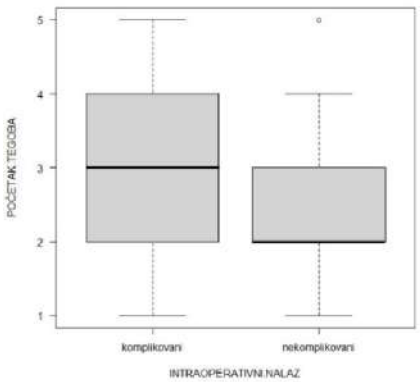
Što se tiče komorbiditeta, ukupno 7 pacijenata (3,02%) bilo je dijagnostikovano sa dijabetes melitusom. Od njih, 5 pacijenata se nalazilo u grupi sa nekoplikovanim

**Figure 1.** The box-plot diagram illustrates the relationship between patient age and intraoperative findings in complicated and uncomplicated appendicitis. The diagram indicates a statistically significant difference in the severity of intraoperative findings between younger and older patients. The central line within each box represents the median age, while the edges of the box denote the first and third quartiles.




In most patients with complicated inflammation, symptoms appeared within 24 to 48 hours prior to establishing the preoperative diagnosis. In contrast, patients with uncomplicated inflammation most commonly experienced symptoms for less than 24 hours before arriving at the hospital. This difference in symptom duration between the two groups was statistically significant ($p < 0.01$), indicating an association between longer symptom duration and the development of complicated disease. These findings highlight the importance of early clinical assessment and intervention to reduce the risk of complications..

**Figure 2.** The box-plot diagram illustrates the relationship between symptom duration and intraoperative findings in complicated and uncomplicated appendicitis. The diagram shows that longer symptom duration is associated with a higher incidence of complicated intraoperative findings. The central line within each box represents the median duration, while the edges of the box denote the first and third quartiles..




A total of 63 patients (27.27%) experienced episodes of elevated body temperature during the course of their symptoms, of whom 26 had complicated and 37 had uncomplicated appendicitis. Considering the difference in group size, the difference in the presence of fever between the groups was statistically significant ($p < 0.01$).

Regarding comorbidities, a total of 7 patients (3.02%) were diagnosed with diabetes

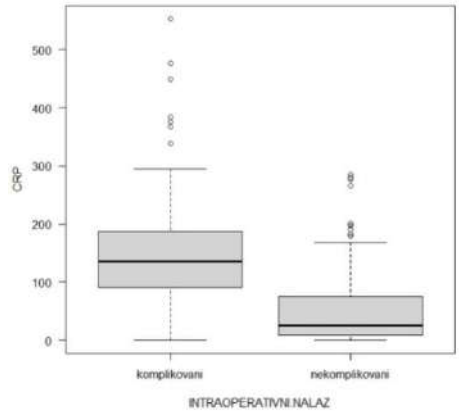
apendicitisom, dok su 2 pacijenta bila u grupi sa komplikovanim apendicitisom. Statistička analiza nije pokazala značajnu razliku u učestalosti dijabetesa između grupa, što ukazuje da u ovom uzorku prisustvo DM nije značajno uticalo na verovatnoću razvoja komplikovanog apendicitisa.

Ultrazvučnim pregledom ustanovljeni su nalazi koji ukazuju na akutni apendicitis kod 134 pacijenta (58,01%), dok 97 pacijenata (41,99%) nije imalo ultrasonografske nalaze bolesti. U grupi pacijenata sa pozitivnim ultrazvučnim nalazima, procenjena je učestalost komplikovanog u odnosu na nekoplikovani apendicitis. Iako je veći procenat pacijenata sa pozitivnim nalazima imao komplikovani apendicitis, razlika između grupa nije bila statistički značajna (p=0,134).

U ovoj studiji, prosečan broj leukocita u perifernoj krvi iznosio je 12,61 × $10^9$/L ± 4,64 × $10^9$/L, što ukazuje da je većina pacijenata imala leukocitozu. Kod pacijenata sa nekoplikovanim apendicitisom, vrednosti leukocita su se kretale od 2,2 × $10^9$/L do 25,2 × $10^9$/L, sa prosečnom vrednošću od 11,8 × $10^9$/L. U grupi sa komplikovanim apendicitisom, leukociti su se kretali od 4,3 × $10^9$/L do 27,8 × $10^9$/L, sa prosekom od 14,4 × $10^9$/L. Uporedna analiza ovog inflamatornog markera između dve grupe pokazala je statistički značajnu razliku (p<0,01).

Vrednosti C-reaktivnog proteina (CRP) među pacijentima su značajno varirale, sa standardnom devijacijom nešto manjom od prosečne vrednosti, i iznosile su 66,62 ± 65,60 mg/L. Koncentracije CRP-a su se kretale od 0,2 mg/L do 265,4 mg/L. Medijana CRP-a kod pacijenata sa nekoplikovanim apendicitisom iznosila je 24,55 mg/L, što je bilo značajno niže od medijane od 109 mg/L kod pacijenata sa komplikovanim apendicitisom.

Slika 3. Prikazom u vidu box-plot dijagrama ilustruje se odnos između nivoa C-reaktivnog proteina (CRP) i intraoperativnih nalaza apendicitisa. Viši nivoi CRP-a povezani su sa težim, komplikovanim oblicima apendicitisa. Središnja linija u svakom boksu predstavlja medijanu vrednost CRP-a, dok ivice boksa označavaju prvi i treći kvartil.




## DISKUSIJA

Preoperativno razlikovanje komplikovanog i nekoplikovanog akutnog apendicitisa i dalje predstavlja veliki klinički izazov, naročito kada su klinički nalazi nejasni, a laboratorijski testovi nedovoljno specifični [11,12]. Ova dijagnostička nesigurnost doprinosi značajnoj stopi pogrešne dijagnoze, koja prema više studija iznosi između 12% i 30% [2,8,10]. Takve greške mogu dovesti do nepotrebne hirurške intervencije ili do kašnjenja u lečenju, što pogoršava ishod lečenja. Stoga je poboljšanje dijagnostičkih alata i kriterijuma ključno za optimizaciju upravljanja bolešću i smanjenje negativnih apendektomija i komplikacija.

Tradicionalno se za nekoplikovani apendicitis preporučuje rana apendektomija kako bi se sprečila ruptura [13]. Međutim, nova randomizirana istraživanja [13–15] i meta-analize [16,17] pokazuju da neoperativno lečenje antibioticima može biti uspešno kod pažljivo odabranih pacijenata sa nekoplikovanim apendicitisom. Prema ažuriranim smernicama Svetskog udruženja za urgentnu hirurgiju (WSES), donetim na Jerusalimskom konsenzusnom sastanku 2020. godine,

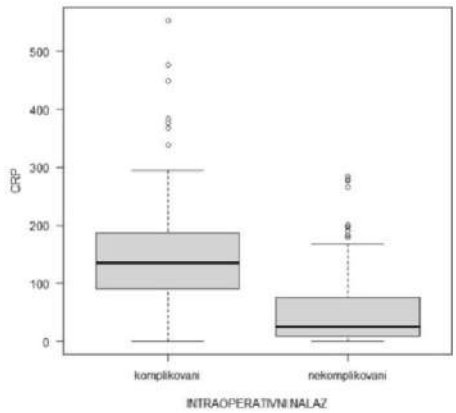
mellitus. Of these, 5 patients were in the uncomplicated appendicitis group, while 2 patients were in the complicated appendicitis group. Statistical analysis did not show a significant difference in the prevalence of diabetes between the groups, suggesting that in this sample, the presence of DM did not significantly influence the likelihood of developing complicated appendicitis.

Ultrasound examination demonstrated findings indicative of acute appendicitis in 134 patients (58.01%), while 97 patients (41.99%) had no ultrasonographic evidence of the disease. Among patients with positive ultrasound findings, the prevalence of complicated versus uncomplicated appendicitis was assessed. Although a higher percentage of patients with positive findings had complicated appendicitis, the difference between the groups was not statistically significant ($p = 0.134$).

In this study, the mean white blood cell count in peripheral blood was $12.61 \times 10^9$/L ± $4.64 \times 10^9$/L, indicating that most patients presented with leukocytosis. In patients with uncomplicated appendicitis, leukocyte values ranged from $2.2 \times 10^9$/L to $25.2 \times 10^9$/L, with a mean of $11.8 \times 10^9$/L. In the complicated appendicitis group, leukocyte counts ranged from $4.3 \times 10^9$/L to $27.8 \times 10^9$/L, with a mean value of $14.4 \times 10^9$/L. Comparative analysis of this inflammatory marker between the two groups demonstrated a statistically significant difference ($p < 0.01$).

C-reactive protein (CRP) values among patients varied considerably, with a standard deviation slightly lower than the mean, amounting to 66.62 ± 65.60 mg/L. CRP concentrations ranged from 0.2 mg/L to 265.4 mg/L. The median CRP level in patients with uncomplicated appendicitis was 24.55 mg/L, which was significantly lower than the median of 109 mg/L observed in patients with complicated appendicitis..

**Figure 3**. The box-plot diagram illustrates the relationship between C-reactive protein (CRP) levels and intraoperative findings in appendicitis. Higher CRP levels are associated with more severe, complicated forms of appendicitis. The central line within each box represents the median CRP value, while the edges of the box denote the first and third quartiles..




## DISCUSSION

Preoperative differentiation between complicated and uncomplicated acute appendicitis remains a major clinical challenge, particularly when clinical findings are unclear and laboratory tests lack sufficient specificity [11,12]. This diagnostic uncertainty contributes to a substantial rate of misdiagnosis, which, according to several studies, ranges between 12% and 30% [2,8,10]. Such errors may lead to unnecessary surgical intervention or delays in treatment, thereby worsening clinical outcomes. Therefore, improving diagnostic tools and criteria is essential for optimizing disease management and reducing negative appendectomies and complications.

Traditionally, early appendectomy has been recommended for uncomplicated appendicitis to prevent rupture [13]. However, recent randomized studies [13–15] and meta-analyses [16,17] show that nonoperative antibiotic treatment may be successful in

antibiotska terapija se preporučuje kao bezbedna i efikasna alternativa hirurškom lečenju kod pacijenata sa nekomplikovanim apendicitisom bez prisustva apendikolitijaze. Važno je napomenuti da nedijagnostikovana perforacija može dovesti do ozbiljnih komplikacija, kao što su apsces i purulentni peritonitis [19]. Stopa rupture u akutnom apendicitisu iznosi između 20% i 34% [20–22]. Kod pacijenata tretiranih neoperativno važno je istaći da postoji približno 39% od rizika od recidiva u roku od 5 godina [14,18].

Laparoskopska apendektomija ostaje zlatni standard u lečenju sumnje na komplikovani apendicitis [23]. Potreba za invazivnijim pristupom opravdana je ozbiljnim komplikacijama koje se mogu javiti, uključujući infekciju, ileus, intraabdominalni apsces i fistule [24–26]. Kašnjenje sa operacijom povećava rizik od životno ugrožavajućih stanja i rehospitalizacije [27].

Demografske karakteristike, naročito starost i pol, pokazale su se kao značajni faktori u razvoju komplikovanog apendicitisa. Birben i saradnici su prijavili veću učestalost komplikovanog apendicitisa kod starijih i muških pacijenata [28]. Naša studija nije pokazala statistički značajnu razliku u polu, ali su pacijenti sa komplikovanim apendicitisom bili značajno stariji. To se može objasniti smanjenjem imunološke funkcije i fizioloških rezervi sa godinama. Brojne studije beleže slične nalaze [2,3,6,29,30].

Dug interval od pojave simptoma do dijagnoze direktno je povezan sa razvojem komplikacija. Naša studija potvrđuje da je duže trajanje simptoma prediktor komplikovanog toka bolesti, u skladu sa prethodnim istraživanjima [2,3,8,23,30,31].

Povišena temperatura (≥37,4°C) je pokazana kao klinički koristan indikator komplikovanog apendicitisa [30,31,33], Naši nalazi, kao i studija Akai i saradnika [34], potvrđuju značaj telesne temperature u proceni težine bolesti.

Iako je dijabetes povezan sa imunološkom disfunkcijom i težim tokom apendicitisa, naša studija nije pokazala značajnu povezanost, verovatno zbog malog broja obolelih od dijabetesa i bolje kontrole bolesti u našoj ustanovi [2,35].

Ultrazvuk je često prvi izbor za dijagnostiku, ali ograničen subjektivnošću interpretacije i telesnim faktorima pacijenta [3,36,37]. Naši rezultati potvrđuju da ultrazvuk nije dovoljan za razlikovanje komplikovanih i nekoplikovanih oblika bolesti i treba ga koristiti u kombinaciji sa kliničkim pregledom i laboratorijskim markerima.

Leukocitoza je značajan, ali nespecifičan marker. Naši rezultati potvrđuju korelaciju sa komplikovanim apendicitisom, ali bez dovoljne prediktivne vrednosti samostalno [4,7,8,27,38].

CRP, kao akutnofazni protein, pokazuje proporcionalno povećanje sa težinom zapaljenja [3,27,29,30,31,33,38,39]. Naša studija je potvrdila njegovu visoku vrednost kod komplikovanih slučajeva (medijana 109 mg/L), što dodatno potvrđuje njegovu dijagnostičku korisnost.

## ZAKLJUČAK

Naša studija potvrđuje da su starija životna dob, povišena telesna temperatura, duže trajanje simptoma i povišene vrednosti CRP-a ključni faktori povezani sa komplikovanim akutnim apendicitisom. CRP se izdvojio kao najpouzdaniji preoperativni biomarker u proceni težine bolesti. Ovi rezultati naglašavaju potrebu za integracijom kliničke evaluacije sa odabranim laboratorijskim parametrima, posebno CRP-om, kako bi se osigurala preciznija preoperativna dijagnoza i primenila pravovremena terapijska strategija.

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carefully selected patients with uncomplicated appendicitis. According to the updated guidelines of the World Society of Emergency Surgery (WSES), established at the Jerusalem Consensus Conference in 2020, antibiotic therapy is recommended as a safe and effective alternative to surgery in patients with uncomplicated appendicitis without appendicolithiasis. It is important to note that unrecognized perforation may lead to severe complications such as abscess formation and purulent peritonitis [19]. The reported perforation rate in acute appendicitis ranges between 20% and 34% [20–22]. Among patients treated nonoperatively, it should be emphasized that there is an approximately 39% risk of recurrence within 5 years [14,18].

Laparoscopic appendectomy remains the gold standard for the management of suspected complicated appendicitis [23]. The need for a more invasive approach is justified by the serious complications that may arise, including infection, ileus, intra-abdominal abscess, and fistula formation [24–26]. Delaying surgery increases the risk of life-threatening conditions and rehospitalization [27].

Demographic characteristics, particularly age and sex, have been identified as significant factors in the development of complicated appendicitis. Birben et al. reported a higher incidence of complicated appendicitis in older and male patients [28]. Our study did not demonstrate a statistically significant sex difference, but patients with complicated appendicitis were significantly older. This may be explained by age-related declines in immune function and physiological reserves. Numerous studies report similar findings [2,3,6,29,30].

A long interval between symptom onset and diagnosis is directly associated with the development of complications. Our study confirms that longer symptom duration is a predictor of complicated disease, consistent with previous research [2,3,8,23,30,31].

Elevated temperature (≥37.4°C) has been shown to be a clinically useful indicator of complicated appendicitis [30,31,33]. Our findings, as well as the study by Akai et al. [34], confirm the significance of body temperature in assessing disease severity.

Although diabetes is associated with immune dysfunction and a more severe course of appendicitis, our study did not show a significant association, likely due to the small number of diabetic patients and better disease control in our institution [2,35].

Ultrasound is frequently the first diagnostic modality, but it is limited by subjective interpretation and patient-related factors [3,36,37]. Our results confirm that ultrasound alone is insufficient for distinguishing complicated from uncomplicated disease and should be used in combination with clinical evaluation and laboratory markers.

Leukocytosis is an important but nonspecific marker. Our results confirm its correlation with complicated appendicitis, although it lacks sufficient standalone predictive value [4,7,8,27,38].

CRP, as an acute-phase protein, exhibits proportional increases with the severity of inflammation [3,27,29,30,31,33,38,39]. Our study confirmed its markedly elevated levels in complicated cases (median 109 mg/L), further supporting its diagnostic utility..

## CONCLUSION

Our study confirms that older age, elevated body temperature, longer symptom duration, and increased CRP levels are key factors associated with complicated acute appendicitis. CRP emerged as the most reliable preoperative biomarker for assessing disease severity. These findings emphasize the need to integrate clinical evaluation with selected laboratory parameters, particularly CRP, to ensure a more accurate preoperative diagnosis and the implementation of timely therapeutic strategies.

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# ULOGA KLINIČKIH I LABORATORIJSKIH PARAMETARA U PROCENI RIZIKA KOD PACIJENATA SA KARDIOVASKULARNIM BOLESTIMA

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**SAŽETAK: Uvod:** Kardiovaskularne, ali i metaboličke bolesti predstavljaju značajan izazov u modernom zdravstvu zbog visokog stepena smrtnosti i uticaja na kvalitet života. Precizna procena rizika je ključna za personalizaciju terapije i sprečavanje komplikacija koja uključuje kliničke, inflamatorne i hemostatske faktore rizika. **Cilj studije** bio je istražiti ulogu kliničkih i laboratorijskih parametara u proceni rizika kod pacijenata sa kardiovaskularnim bolestima, sa posebnim fokusom na inflamatorne i hemostatske indekse poput odnosa neutrofili-limfociti (*Neutrophil-Lymphocyte ratio* - NLR), srednjeg volumena trombocita (*Mean Platelet Volume* - MPV) i dijametra eritrocita u odnosu na trombocite (*Red cell distribution width to Platelet Ratio* - RPR). **Ispitanici i metode:** Studija je sprovedena na 311 pacijenata sa kardiovaskularnim bolestima. Korišćene su retrospektivne i prospektivne metode za prikupljanje kliničkih i laboratorijskih podataka, uključujući indeks telesne mase , krvni pritisak i lipidni profil. Statistička analiza obuhvatila je faktorsku analizu i višestruku linearnu regresiju. **Rezultati:** U ovoj studiji utvrđeno je da su klinički i laboratorijski parametri, uključujući LDL holesterol, kao i inflamatorno-hemostatski indeksi srednji volumen trombocita (MPV) kao i odnos dijametara eritrocita u odnosu na trombocite (RPR), značajno povezani sa prisustvom i kombinacijama kardiovaskularnih bolesti. Indeks dijametra eritrocita u odnosu na trombocite je bio najviši kod pacijenata sa hipertenzijom i stentom ($p<0,001$), što ukazuje na povećanu prokoagulabilnost i inflamatorni status u ovim grupama. Faktorska analiza je izdvojila tri glavna faktora, od kojih je starost-hematološki faktor jedini pokazao statistički značajnu povezanost sa kardiovaskularnim bolestima ($p=0,008$), potvrdivši njegovu prediktivnu vrednost. **Zaključak:** Na osnovu ovih nalaza može se zaključiti da integracija kliničkih i laboratorijskih pokazatelja, sa posebnim akcentom na inflamatorno-hemostatske indekse i starosno-hematološke varijable, omogućava raniju identifikaciju pacijenata sa visokim rizikom i predstavlja osnovu za razvoj personalizovanih terapijskih strategija.
**Ključne reči**: klinički parametri, laboratorijski parametri, kardiovaskularne bolesti

## UVOD

Kardiovaskularne (KVB), ali i metaboličke bolesti predstavljaju jedan od najznačajnijih izazova modernog zdravstva, sa visokim stepenom smrtnosti i ozbiljnim uticajem na kvalitet života obolelih. Ove bolesti obuhvataju širok spektar stanja, uključujući koronarnu bolest srca (KBS), arterijsku hipertenziju (HTA) i dislipidemiju (DLD), koja često koegzistiraju i međusobno se uslovljavaju [1]. Prema podacima Svetske zdravstvene organizacije, kardiovaskularne bolesti su vodeći uzrok smrti na globalnom nivou, što dodatno naglašava potrebu za efikasnim strategijama prevencije i lečenja [2]. Kardiometabolički sindrom predstavlja savremenu epidemiju koja može da predvidi ukupnu i kardiovaskularnu smrtnost, incidencu i progresiju koronarne i karotidne ateroskleroze, kao i iznenadnu smrt, nezavisno od drugih kardiovaskularnih rizika [3]. Nedavno je primećen značajan porast incidencije komorbiditeta između metaboličkih poremećaja i kardiovaskularnih bolesti (KVB), posebno u populacijama sa rizikom za metabolički sindrom ili pre-metabolički sindrom [4]. Osobe sa metaboličkim sindromom (MetS) imaju trostruko veći relativni rizik od srčanog udara ili moždanog udara, dvostruko veći rizik od KVB ili smrti od takvih događaja i petostruko veći rizik od razvoja Diabetes Mellitus tip 2 (DM2) kod oba pola u poređenju sa ljudima koji ga nemaju [5-7]. Istraživanja pokazuju da skoro polovina pacijenata sa koronarnom bolešću srca (KBS) ispunjava kriterijume za metabolički sindrom (MetS) [5,7,8]. Jedna studija je pokazala jasnu povezanost između kumulativne izloženosti metaboličkim poremećajima i infarkta miokarda (IM), kao i značaj upravljanja


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# THE ROLE OF CLINICAL AND LABORATORY PARAMETERS IN RISK ASSESSMENT OF PATIENTS WITH CARDIOVASCULAR DISEASES

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**SUMMARY: Introduction:**Cardiovascular and metabolic diseases represent a significant challenge in modern healthcare due to their high mortality rates and impact on quality of life. Accurate risk assessment is essential for therapy personalization and the prevention of complications, encompassing clinical, inflammatory, and hemostatic risk factors. The aim of this study was to investigate the role of clinical and laboratory parameters in risk assessment among patients with cardiovascular diseases, with a particular focus on inflammatory and hemostatic indices such as the Neutrophil-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV), and the Red Cell Distribution Width to Platelet Ratio (RPR). Subjects and Methods: The study included 311 patients with cardiovascular diseases. Retrospective and prospective methods were used to collect clinical and laboratory data, including body mass index, blood pressure, and lipid profile. Statistical analysis comprised factor analysis and multiple linear regression. Results: The study demonstrated that clinical and laboratory parameters, including LDL cholesterol, as well as inflammatory-hemostatic indices such as MPV and RPR, were significantly associated with the presence and combinations of cardiovascular diseases. The RPR index was highest in patients with hypertension and stents ($p < 0.001$), indicating increased procoagulability and inflammatory status in these groups. Factor analysis identified three main factors, of which the age-hematological factor was the only one showing a statistically significant association with cardiovascular diseases ($p = 0.008$), confirming its predictive value. Conclusion: These findings suggest that the integration of clinical and laboratory indicators, with a particular emphasis on inflammatory-hemostatic indices and age-hematological variables, allows for earlier identification of high-risk patients and provides a foundation for the development of personalized therapeutic strategies.

**Keywords**: clinical parameters, laboratory parameters, cardiovascular diseases

## INTRODUCTION

Cardiovascular (CVD), as well as metabolic diseases, represent one of the most significant challenges in modern healthcare, due to their high mortality rates and severe impact on patients' quality of life. These conditions encompass a wide range of disorders, including coronary artery disease (CAD), arterial hypertension (HTN), and dyslipidemia (DLD), which often coexist and influence each other [1]. According to the World Health Organization, cardiovascular diseases are the leading cause of death globally, further emphasizing the need for effective prevention and treatment strategies [2].

Cardiometabolic syndrome represents a contemporary epidemic that can predict overall and cardiovascular mortality, the incidence and progression of coronary and carotid atherosclerosis, as well as sudden death, independently of other cardiovascular risk factors [3]. A significant increase has recently been observed in the incidence of comorbidities between metabolic disorders and cardiovascular diseases, particularly in populations at risk for metabolic syndrome or pre-metabolic syndrome [4]. Individuals with metabolic syndrome (MetS) have a threefold higher relative risk of myocardial infarction or stroke, a twofold higher risk of CVD or death from such events, and a fivefold higher risk of developing type 2 diabetes mellitus (T2DM) in both sexes compared to those without the syndrome [5–7].

Research indicates that nearly half of patients with coronary artery disease meet the criteria for metabolic syndrome [5,7,8]. One study demonstrated a clear association between cumulative exposure to metabolic disorders and

metaboličkim poremećajima u prevenciji KVB [9]. Druga studija je otkrila pozitivnu povezanost između kumulativnih metaboličkih opterećenja i rizika od razvoja atrijalne fibrilacije (AF) [10]. Podsticanje aktivnog načina života može poboljšati metaboličke poremećaje kod nekih pacijenata i pomoći u kontroli krvnog pritiska [11]. Pojedinačne komponente MetS i integralno MetS povećavaju rizik od srčane insuficijencije (SI) i ishemijskog moždanog udara [12]. Faktori obrnute uzročnosti nisu mogli biti adekvatno uzeti u obzir u opservacionim studijama, te stoga uzročna veza između metaboličkih poremećaja i različitih KVB ostaje neizvesna [13].

Važnost procene rizika kod pacijenata sa kardiovaskularnim bolestima i metaboličkim poremećajima ogleda se u mogućnosti prepoznavanja visokorizičnih pojedinaca, što omogućava pravovremenu intervenciju i prilagođavanje terapijskih strategija. Stratifikacija rizika koristeći SCORE-2 (Systematic Coronary Risk Evaluation) omogućava procenu 10-godišnjeg rizika od kardiovaskularnih događaja, kao što su infarkt miokarda i moždani udar. Ovaj alat uzima u obzir faktore kao što su starost, pol, krvni pritisak, nivo holesterola, pušenje i prisustvo dijabetesa. U savremenoj medicinskoj praksi, procena rizika korišćenjem SCORE 2 (Systematic Coronary Risk Evaluation) i SCORE2-OP za starije pacijente [14,15] predstavlja esencijalan aspekt u donošenju kliničkih odluka. Ovaj pristup omogućava razvijanje individualizovanih planova terapije i preventive, čime se značajno smanjuje ukupan rizik od ozbiljnih kardiovaskularnih događaja. Korišćenje ovog alata, omogućava preciznije identifikovanje pacijente sa višim rizikom i implementirati odgovarajuće intervencije, što doprinosi unapređenju zdravstvenih ishoda. Kao što je napomenuto, procena rizika kod pacijenata sa kardiovaskularnim, ali i metaboličkim bolestima predstavlja fundamentalnu komponentu modernog pristupa kliničkoj medicini, s obzirom na sveprisutnost ovih stanja i njihov značajan doprinos morbiditetu i mortalitetu širom sveta. Kardiovaskularne bolesti, uključujući ishemijsku srčanu bolest i cerebrovaskularne bolesti, često su u udruženosti sa metaboličkim poremećajima, kao što su dijabetes melitus (DM) i metabolički sindrom (MetS). Ova udruženost se ogleda u zajedničkim patofiziološkim mehanizmima, što dodatno komplikuje dijagnostiku i lečenje. Klinički parametri, uključujući, ali ne ograničavajući se na, krvni pritisak, lipidni profil, nivo glukoze u krvi, indeks telesne mase (BMI), kao i markere upale, služe kao osnova za stratifikaciju rizika i personalizaciju terapijskih strategija [16]. Analiza ovih međusobno povezanih parametara omogućava identifikaciju pojedinaca sa višestrukim faktorima rizika, koji se često klasifikuju kao veoma visok rizik, što je ključno za sprovođenje preventivnih intervencija. Uloga svakog od ovih kliničkih pokazatelja ne može se preceniti, jer oni ne samo da pomažu u proceni trenutnog zdravstvenog stanja pacijenta, već takođe omogućavaju predikciju budućih kardiovaskularnih događaja. Shodno navedenom, posmatranje kompleksnosti ovih parametara i njihovih međusobnih odnosa može značajno doprineti unapređenju strategija prevencije i lečenja. Starost je najjači nepromenljivi faktor rizika za KVB. Povećanje kardiovaskularnog rizika je kontinuirano i progresivno kod muškaraca ili žena. Međutim, izgleda da se prelazak u kategoriju visokog rizika za razvoj kardiovaskularnih bolesti dešava u određenom uzrastu za svaki pol [17]. Uzimajući u obzir rizik procenjen na preko 20% za 10 godina za kompozitni ishod IM, moždanog udara i smrti iz bilo kog uzroka, prelazak u kategoriju visokog rizika dogodio se sa 48 godina kod muškaraca i 54 godine kod žena. Kada je šira definicija KVB uključivala revaskularizaciju, starosna dob tranzicije pala je na 41 i 48 godina za muškarce i žene, respektivno. Prelazak iz kategorije niskog u umereni rizik dogodio se sa 35 i 45 godina i za muškarce i za žene s obzirom na širu definiciju [17]. U opštoj populaciji, incidencija IM veća je kod muškaraca nego kod žena, sa koeficijentom rizika prilagođenom uzrastu [17]. Studija autora Cai i saradnika koja je uključivala 10 opservacionih studija sa ukupno 166.027 pacijenata sa Diabetes Mellitus tip 1 (DMT1), izveden je zaključak da je među tim pacijentima relativan rizik od mortaliteta bio 5,09, od KBS je 9,38, IM 6,37, AF 1,36, moždanog udara 4,08 što je dalje ukazalo da je relativno povećan rizik kod žena za KBS, KVB, IM i moždani udar povezan sa DMT1 [18]. Dakle, kod žena sa DM tip 1, relativni rizik za fatalni koronarni događaj je 50% veći nego kod muškaraca. Ovaj fenomen može se delimično objasniti manje povoljnim profilom kardiovaskularnog rizika kod žena, koji je povezan sa hipertenzijom (HTA) i hiperlipidemijom. Takođe, važno je razmotriti da li hormonalne promene tokom menopauze

myocardial infarction, highlighting the importance of managing metabolic disorders for CVD prevention [9]. Another study revealed a positive correlation between cumulative metabolic burdens and the risk of developing atrial fibrillation (AF) [10]. Promoting an active lifestyle can improve metabolic disorders in some patients and aid in blood pressure control [11]. Both individual components of MetS and MetS as a whole increase the risk of heart failure (HF) and ischemic stroke [12]. Reverse causation factors could not be adequately accounted for in observational studies, and therefore the causal relationship between metabolic disorders and various CVDs remains uncertain [13].

The importance of risk assessment in patients with cardiovascular and metabolic disorders lies in the ability to identify high-risk individuals, allowing timely intervention and tailored therapeutic strategies. Risk stratification using SCORE-2 (Systematic Coronary Risk Evaluation) enables the estimation of 10-year risk for cardiovascular events, such as myocardial infarction and stroke. This tool takes into account factors including age, sex, blood pressure, cholesterol levels, smoking status, and the presence of diabetes. In modern medical practice, risk assessment using SCORE-2 and SCORE2-OP for older patients [14,15] represents an essential component of clinical decision-making. This approach facilitates the development of individualized therapy and prevention plans, thereby significantly reducing the overall risk of serious cardiovascular events. The use of this tool allows for more accurate identification of high-risk patients and the implementation of appropriate interventions, contributing to improved health outcomes.

As noted, risk assessment in patients with cardiovascular and metabolic diseases constitutes a fundamental aspect of contemporary clinical medicine, given the prevalence of these conditions and their significant contribution to morbidity and mortality worldwide. Cardiovascular diseases, including ischemic heart disease and cerebrovascular disorders, are frequently associated with metabolic disturbances such as diabetes mellitus (DM) and metabolic syndrome (MetS). This association is reflected in shared pathophysiological mechanisms, which further complicates diagnosis and management. Clinical parameters, including—but not limited to—blood pressure, lipid profile, blood glucose levels, body mass index (BMI), and inflammatory markers, serve as the basis for risk stratification and the personalization of therapeutic strategies [16].

Analysis of these interrelated parameters allows for the identification of individuals with multiple risk factors, who are often classified as very high risk, which is crucial for the implementation of preventive interventions. The role of each of these clinical indicators cannot be overstated, as they not only help assess the patient's current health status but also enable the prediction of future cardiovascular events. Accordingly, monitoring the complexity of these parameters and their interactions can significantly enhance prevention and treatment strategies.

Age is the strongest non-modifiable risk factor for CVD. The increase in cardiovascular risk is continuous and progressive in both men and women. However, the transition to the high-risk category for the development of cardiovascular disease appears to occur at specific ages for each sex [17]. Considering a risk estimated at over 20% for 10 years for the composite outcome of myocardial infarction, stroke, and all-cause mortality, the transition to high risk occurred at 48 years for men and 54 years for women. When the broader definition of CVD included revascularization, the age of transition decreased to 41 and 48 years for men and women, respectively. The transition from low to moderate risk occurred at 35 and 45 years for men and women, respectively, according to the broader definition [17]. In the general population, the incidence of myocardial infarction is higher in men than in women, with age-adjusted risk coefficients [17].

A study by Cai et al., which included 10 observational studies with a total of 166,027 patients with type 1 diabetes mellitus (T1DM), concluded that among these patients, the relative risk of mortality was 5.09; for coronary artery disease 9.38; myocardial infarction 6.37; atrial fibrillation 1.36; and stroke 4.08. This further indicated that the relatively increased risk for CAD, CVD, myocardial infarction, and stroke was higher in women with T1DM [18]. Thus, women with type 1 diabetes have a 50% higher relative risk for fatal coronary events

dodatno utiču na povećanje ovog rizika, s obzirom na to da smanjenje nivoa estrogena može negativno uticati na kardiovaskularno zdravlje žena.

HTA je dobro utvrđen faktor rizika za kardiovaskularne bolesti i za smrtnost od moždanog udara. Izolovana sistolna HTA je glavni faktor rizika za KBS u svim uzrastima, i kod muškaraca i kod žena [19,20].

LDL je jedan od najvažnijih reverzibilnih faktora rizika za kardiovaskularni morbiditet i mortalitet.

Podaci o kardiovaskularnom mortalitetu iz pomoćne opservacione MRFIT studije [21], u eri pre statina, pokazali su da je među 342.815 muškaraca srednjih godina u SAD (od kojih je 5,163 imalo DM) koji su praćeni 16 godina, apsolutni prilagođeni rizik od smrti od kardiovaskularnih bolesti, stratifikovan prema nivou LDL holesterola, bio značajno veći kod pacijenata sa DM. Naime, rizik od kardiovaskularnog mortaliteta bio je između 2,83 i 4,46 puta veći kod pacijenata sa DM u poređenju sa onima koji nisu imali DM, što ukazuje na važnost LDL stratifikacije kao ključnog faktora rizika u ovoj populaciji [34]. Stratifikacija LDL holesterola se obično deli u nekoliko kategorija kao optimalno: manje od 100 mg/dL, skoro optimalno: 100-129 mg/dL, granica visoka: 130-159 mg/dL, visoka: 160-189 mg/dL i veoma visoka: 190 mg/dL i više. Pacijenti sa DM često imaju povišene nivoe LDL holesterola, što dodatno povećava rizik od razvoja kardiovaskularnih bolesti. Preporučuje se redovno praćenje i upravljanje nivoima LDL holesterola kod ovih pacijenata kako bi se smanjio rizik od kardiovaskularnih događaja. Podaci o kardiovaskularnom mortalitetu iz pomoćne opservacione MRFIT studije [21], u eri pre statina, pokazali su da je među 342.815 muškaraca srednjih godina u SAD (od kojih je 5.163 imalo DM) koji su praćeni 16 godina, apsolutni prilagođeni rizik od smrti od KVB, stratifikovan prema nivou holesterola, bio nekoliko puta veći kod pacijenata sa DM nego kod pacijenata koji nisu imali DM. Povećanje smrtnosti od KVB je bilo nesrazmerno veće kod pacijenata sa DM, što sugeriše da je holesterol snažan i nezavistan faktor rizika za smrtnost od KVB, koju potencira DM. Međutim, postavlja se pitanje: šta je jači faktor—DM ili LDL holesterol? Iako oba faktora igraju značajnu ulogu, istraživanja sugerišu da DM može imati jači uticaj na kardiovaskularni ishod, posebno kada se uzmu u obzir dodatni faktori kao što su inflamacija i metabolički poremećaji koji su prisutni kod pacijenata sa DM [35]. Prema istraživanju Zhang i saradnika hronična inflamacija intime krvnih sudova niskog stepena kod pacijenata sa dijabetesom tipa 2 dodatno povećava rizik od kardiovaskularnih bolesti, dok istraživanje Chena i saradnika naglašava da agonisti GLP-1 značajno smanjuju kardiovaskularne događaje u ovoj populaciji, sugerišući da DM ima jači uticaj na kardiovaskularne ishode [35,36]. Uzimajući u obzir smanjenje LDL-a statinima, studija Hodkinsona i saradnika pokazuje da će smanjenje LDL-a za 1 mmol/L sa statinom smanjiti relativni rizik KVB za jednu petinu. Takođe, studija navodi da se linearni fenomen može pojaviti na sličan način na bilo kom nivou početne vrednosti LDL-a, barem do 1,293 mmol/L (što odgovara 50 mg/dL) [22]. Prema pomenutoj studiji kod pacijenata sa DM, statini promovišu proporcionalno smanjenje od 9% mortaliteta od svih uzroka ($p=0,02$) i od 21% incidencije velikih vaskularnih događaja ($p<0,0001$) po svakom mmol/l smanjenja LDL-ac. Osim toga, postoji i značajno smanjenje akutnog IM ($p<0,0001$), koronarne revaskularizacije ($p<0,0001$) i moždanog udara ($p<0,0002$).

Cilj ovog rada je istražiti povezanost između kliničkih i laboratorijskih parametara, sa posebnim naglaskom na inflamatorno-hemostatske indekse, u predviđanju rizika od kardiovaskularnih bolesti. Ovaj rad takođe ima za cilj da identifikuje ključne faktore koji mogu doprineti ranom prepoznavanju pacijenata sa visokim rizikom, kako bi se omogućila pravovremena intervencija i prilagođena terapija.

## MATERIJAL I METODE

Ovo istraživanje je realizovano kao kombinovana retrospektivno-prospektivna transverzalno-longitudinalna kohortna studija u Domu zdravlja Pirot, u periodu od 1.1.2024. do 1.6.2024. godine. U retrospektivnom delu analizirani su elektronski zdravstveni kartoni pacijenata radi prikupljanja podataka o demografskim karakteristikama, pušačkom statusu, farmakoterapiji u prethodnih šest meseci i laboratorijskim nalazima ne starijim od šest meseci. U prospektivnom delu sistematski su prikupljani novi podaci o antropometrijskim merama i vrednostima arterijskog pritiska

compared to men. This phenomenon may be partly explained by a less favorable cardiovascular risk profile in women, associated with hypertension (HTN) and hyperlipidemia. It is also important to consider whether hormonal changes during menopause further contribute to this increased risk, given that decreased estrogen levels may negatively affect women's cardiovascular health.

Hypertension (HTN) is a well-established risk factor for cardiovascular diseases (CVD) and stroke-related mortality. Isolated systolic hypertension is a major risk factor for coronary artery disease (CAD) across all age groups and in both men and women [19,20].

LDL cholesterol is one of the most important modifiable risk factors for cardiovascular morbidity and mortality. Data from the supplementary observational MRFIT study [21], conducted in the pre-statin era, showed that among 342,815 middle-aged men in the United States (of whom 5,163 had diabetes mellitus, DM) followed for 16 years, the absolute adjusted risk of death from CVD, stratified by LDL cholesterol level, was significantly higher in patients with DM. Specifically, the risk of cardiovascular mortality was between 2.83 and 4.46 times higher in patients with DM compared to those without DM, highlighting the importance of LDL stratification as a key risk factor in this population [34]. LDL cholesterol is commonly stratified into the following categories: optimal (<100 mg/dL), near optimal (100–129 mg/dL), borderline high (130–159 mg/dL), high (160–189 mg/dL), and very high (≥190 mg/dL). Patients with DM often present with elevated LDL cholesterol levels, further increasing their risk for developing cardiovascular disease. Regular monitoring and management of LDL cholesterol in these patients are recommended to reduce the risk of cardiovascular events. The MRFIT study [21] also demonstrated that the increase in CVD mortality was disproportionately higher in patients with DM, suggesting that cholesterol is a strong and independent risk factor for CVD mortality, potentiated by DM. However, the question arises: which is the stronger risk factor—DM or LDL cholesterol? While both factors play a significant role, research suggests that DM may exert a stronger influence on cardiovascular outcomes, particularly when considering additional factors such as inflammation and metabolic disturbances present in patients with DM [35]. According to Zhang et al., chronic low-grade inflammation of the vascular intima in patients with type 2 diabetes further increases the risk of CVD, while Chen et al. highlighted that GLP-1 agonists significantly reduce cardiovascular events in this population, suggesting that DM has a stronger impact on cardiovascular outcomes [35,36]. Considering LDL reduction with statins, the study by Hodkinson et al. showed that lowering LDL by 1 mmol/L with a statin reduces relative CVD risk by one-fifth. The study also indicates that this linear phenomenon can occur similarly at any baseline LDL level, at least down to 1.293 mmol/L (50 mg/dL) [22]. In patients with DM, statins promote a proportional reduction of 9% in all-cause mortality ($p=0.02$) and 21% in major vascular events ($p<0.0001$) per mmol/L reduction in LDL-C. Additionally, there is a significant reduction in acute myocardial infarction ($p<0.0001$), coronary revascularization ($p<0.0001$), and stroke ($p<0.0002$).

The aim of this study is to investigate the relationship between clinical and laboratory parameters, with a particular focus on inflammatory-hemostatic indices, in predicting cardiovascular risk. This work also seeks to identify key factors that may facilitate the early recognition of high-risk patients, enabling timely intervention and tailored therapy..

## MATERIAL AND METHODS

This research was conducted as a combined retrospective-prospective, cross-sectional, longitudinal cohort study at the Pirot Health Center, during the period from January 1, 2024, to June 1, 2024. In the retrospective part, patients' electronic health records were analyzed to collect data on demographic characteristics, smoking status, pharmacotherapy over the previous six months, and laboratory results not older than six months. In the prospective part, new data on anthropometric measurements and blood pressure values were systematically collected during each patient visit. The study was conducted in accordance with the Helsinki Declaration, and ethical approval was obtained

prilikom svake posete pacijenta. Studija je sprovedena po Helsinškoj deklaraciji, a etičko odobrenje je dobijeno od Etičkog odbora Doma zdravlja Pirot, u Pirotu (poziv na broj: 02-15/EO).

U studiju je uključeno 311 pacijenata starijih od 40 godina, sa prethodno dijagnostikovanim dijabetesom tip 2 i/ili kardiovaskularnim bolestima (koronarna bolest srca, arterijska hipertenzija, angina pectoris, atrijalna fibrilacija, ugrađeni stent). Svi pacijenti su imali dijabetes duže od 5 godina, čime se osigurava relevantnost rezultata. Izuzeti su pacijenti sa malignim bolestima, hroničnom bubrežnom insuficijencijom, akutnim infekcijama, trudnice i oni kod kojih je došlo do promene terapije u poslednjih šest meseci. Svi ispitanici su dali pismeni informisani pristanak.

Kontrolna grupa obuhvatila je pacijente sa dijabetesom tip 2 bez dokazanih kliničkih ili instrumentalno potvrđenih kardiovaskularnih događaja (n=52), koji su služili kao referentna podgrupa za poređenje sa ostalim kohortama. Za svakog pacijenta koji je ispunio kriterijume uključenja i pristao da učestvuje u istraživanju iz elektronskog zdravstvenog kartona prikupljeni su podaci o uzrastu, polu, pušačkom statusu i vrednostima laboratorijskih parametara koji nisu stariji od 6 meseci: hematološki parametri - ukupan broj leukocita, neutrofila, limfocita, eritrocita i trombocita, Biohemijski parametri - glukoza, glikozilirani hemoglobin A1c (HbA1c), ukupni holesterol, lipoproteini niske gustine (*low-density lipoprotein cholesterol,* LDL-C), lipoproteini visoke gustine (*high-density lipoprotein cholesterol,* HDL-C), trigliceridi, urea i kreatinin, inflamatorni markeri - stepen inflamacije je procenjivan kroz odnos ukupnog broja neutrofili-limfociti (*Neutrofil-Lymphocyte ratio* - NLR), odnos širine distribucije eritrocita i ukupnog broja trombocita (*Red Cell Distribution Width to Platelet Count Ratio* - RPR) kao i odnos srednjeg volumena trombocita i ukupnog broja trombocita (*Mean Platelet Volume to Platelet Ratio* - MPR).

Kontinuirane promenljive testirane su Kolmogorov-Smirnov testom normalnosti. Za upoređivanje više grupa korišćen je Kruskal-Wallis test (neparametrijski test koji ne zahteva normalnost distribucije obzirom na to da je u studiji sprovedena faktorska analiza), uz post-hoc Mann-Whitney U test sa Bonferroni korekcijom. Kategorijalne promenljive poređivane su Chi-kvadrat ili Fisherovim egzakt testom, gde je to bilo primenjivo. Za smanjenje dimenzionalnosti sprovedena je faktorska analiza glavnih komponenti (PCA) uz Kaiser-Meyer-Olkin test (>0,50) i Bartlettov test sferičnosti ($p<0,05$), Varimax rotaciju i izdvajanje faktora sa sopstvenim vrednostima >1,0. Prediktori su procenjeni binarnom logističkom regresijom, a za modelovanje zavisnih indeksa MPR i RPR primenjena je višestruka linearna regresija. Svi testovi su bili dvosmerni, a p-vrednost <0,05 smatrana je statistički značajno.

U metodologiji su parametri iz Tabele 1. korišćeni za procenu različitih kombinacija kardiovaskularnih bolesti i metaboličkih poremećaja i analizirani su ključni **demografski** (pol - procenat muškaraca i žena u različitim grupama i starost - prosečna starost pacijenata u svakoj grupi), **klinički** (BMI - indeks telesne mase za svaku grupu, krvni pritisak - sistolički i dijastolički u različitim grupama pacijenata, pušenje - procenat pacijenata koji puše) i **biohemijski parametri** (glukoza i HbA1c - prosečne vrednosti za pacijente sa dijabetesom, hipertenzijom i njihovim kombinacijama, ukupni Holesterol, LDL-C, HDL-C (prosečne vrednosti za različite grupe), trigliceridi - prosečne vrednosti) koji mogu imati značajnu ulogu u stratifikaciji rizika kod pacijenata.

Važno je naglasiti p-vrednosti koje pokazuju statističke razlike između različitih grupa, kao što je označeno sa "p" u poslednjoj koloni. Ove vrednosti su bitne za razumevanje razlika između grupa pacijenata sa različitim metaboličkim poremećajima i kardiovaskularnim bolestima.

from the Ethics Committee of the Pirot Health Center, Pirot (reference number: 02-15/EO).

The study included 311 patients over 40 years of age with previously diagnosed type 2 diabetes mellitus (T2DM) and/or cardiovascular diseases (coronary artery disease, arterial hypertension, angina pectoris, atrial fibrillation, or implanted stent). All patients had diabetes for more than five years, ensuring the relevance of the results. Exclusion criteria included patients with malignancies, chronic kidney disease, acute infections, pregnant women, and those who had undergone therapy changes within the last six months. All participants provided written informed consent.

The control group consisted of patients with T2DM without clinically or instrumentally confirmed cardiovascular events (n=52), serving as a reference subgroup for comparison with other cohorts. For each patient who met the inclusion criteria and agreed to participate in the study, data were collected from electronic health records regarding age, sex, smoking status, and laboratory parameters not older than six months, including:

Hematological parameters: total leukocyte count, neutrophils, lymphocytes, erythrocytes, and platelets.

Biochemical parameters: glucose, glycated hemoglobin A1c (HbA1c), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, urea, and creatinine.

Inflammatory markers: inflammation was assessed through the neutrophil-to-lymphocyte ratio (NLR), red cell distribution width to platelet count ratio (RPR), and mean platelet volume to platelet ratio (MPR).

Continuous variables were tested for normality using the Kolmogorov-Smirnov test. For comparisons between multiple groups, the Kruskal-Wallis test was applied (a non-parametric test that does not require normal distribution, as factor analysis was conducted in the study), followed by post hoc Mann-Whitney U tests with Bonferroni correction. Categorical variables were compared using the Chi-square test or Fisher's exact test, where applicable. To reduce dimensionality, principal component analysis (PCA) was performed, with the Kaiser-Meyer-Olkin (KMO) test (>0.50) and Bartlett's test of sphericity ($p<0.05$), Varimax rotation, and extraction of factors with eigenvalues >1.0. Predictors were assessed using binary logistic regression, and multiple linear regression was applied for modeling dependent indices MPR and RPR. All tests were two-sided, and a p-value <0.05 was considered statistically significant.

In the methodology, the parameters listed in Table 1 were used to evaluate different combinations of cardiovascular diseases and metabolic disorders. Key demographic (sex – percentage of men and women in different groups; age – mean age of patients in each group), clinical (BMI – body mass index for each group; blood pressure – systolic and diastolic values in different patient groups; smoking – percentage of smokers), and biochemical parameters (glucose and HbA1c – mean values for patients with diabetes, hypertension, and their combinations; total cholesterol, LDL-C, HDL-C – mean values for different groups; triglycerides – mean values) were analyzed for their potential significance in risk stratification.

It is important to emphasize the p-values indicating statistically significant differences between groups, as shown in the last column ("p"). These values are essential for understanding differences among patient groups with various metabolic disorders and cardiovascular diseases.

**REZULTATI**

**Tabela 1.** Osnovni klinički i biohemijski podaci pacijenata sa različitim metaboličkim i KVB kao i njihovim kombinacijama (DM, HTA, DM+HTA, HTA + ugrađen stent, DM + ugrađen stent, DM + angina pectoris/aritmija

| Parametri | DM (n=52) | DM+HTA (n=139) | HTA (n=55) | HTA+stent (n=11) | DM+stent (n=19) | DM+AP/AF (n=29) | P |
|---|---|---|---|---|---|---|---|
| Pol (m/ž), n(%) | 31/21 (59.6/40.4) | 64/75 (46.0/54.0) | 16/39 (29.1/70.9) | 6/5 (54.5/45.5) | 15/4 (78.9/21.1) | 11/18 (37.9/62.1) | 19.7, 0.003 |
| Starost (godine) | 58 (46-66) | 68 (62-72)$^{aaa}$ | 68 (62-74)$^{aaa}$ | 72 (66-79)$^{aa}$ | 68 (61-73)$^{aa}$ | 68 (64-74)$^{aaa}$ | <0.001 |
| BMI ($kg/m^2$) | 26.7 (24.0-29.5) | 28.6$^{aa}$ (26.1-31.9) | 27.5 (25.1-31.9) | 28.2 (25.7-31.6) | 27.8 (25.2-30.8) | 29.5 (26.9-32.6) | 0.080 |
| Sistolni pritisak (mm Hg) | 129 (125-132) | 135 (130-140)$^{aaa}$ | 135 (130-145)$^{aa}$ | 130 (130-138) | 130 $^{b,c}$ (120-135) | 130 (120-145) | 0.001 |
| Dijastolni pritisak (mm Hg) | 82 (80-85) | 83 (80-86) | 84 (78-86) | 85 (75-88) | 80 (70-85) | 80 (75-85) | 0.536 |
| Pušenje, ne/da, n (%) | 46/6 (18.6/10.3) | 110/29 (44.5/50.0) | 41/14 16.6/24.1) | 10/1 (4.0/1.7) | 16/3 (6.5/5.2) | 24/5 (9.7/8.6) | 4.9, 0.560 |
| Šećer (mmol/L) | 6.6 (5.5-8.8) | 6.8 (5.6-8.4) | 5.5 $^{aaa,bbb}$ (4.9-5.7) | 4.9 $^{aa,bbb}$ (4.8-5.3) | 6.7 $^{ccc,ddd}$ (6.4-7.3) | 6.4 $^{ccc,ddd}$ (5.3-8.0) | <0.001 |
| HbA1c (%) | 7.1 (6.2-7.9) | 6.5 (6.1-7.5) | 5.8 $^{aaa,bbb}$ (5.7-5.9) | 6.2 $^{c}$ (6.1-6.3) | 6.4 $^{ccc}$ (6.2-8.0) | 6.4 $^{cc}$ (5.9-7.0) | <0.001 |
| Holesterol, ukupni (mmol/L) | 5.07 (4.39-5.76) | 5.09 (4.28-5.97) | 5.72 $^{a,b}$ (4.92-6.12) | 5.39 (4.65-5.97) | 4.60 $^{c}$ (4.15-5.65) | 4.88 $^{cc}$ (4.36-5.40) | 0.047 |
| LDL-C (mmol/L) | 2.86 (2.30-3.72) | 2.71 (2.15-3.53) | 3.55 $^{aa,bbb}$ (2.88-3.90) | 2.48 (2.34-3.31) | 2.46 $^{cc}$ (1.96-2.73) | 2.68 $^{cc}$ (2.03-3.18) | 0.001 |
| HDL-C (mmol/L) | 1.25 (1.03-1.56) | 1.25 (1.06-1.51) | 1.42 $^{b}$ (1.16-1.66) | 1.36 (1.28-1.90) | 1.19 (1.05-1.39) | 1.33 (1.19-1.68) | 0.112 |
| Trigliceridi (mmol/L) | 1.54 (1.06-2.38) | 1.90 $^{a}$ (1.40-2.67) | 1.53 $^{bbb}$ (1.21-1.87) | 1.67 (1.15-2.50) | 1.65 (1.18-3.33) | 1.57 $^{bb}$ (1.05-2.10) | 0.003 |
| RPR indeks | 0.051 (0.044-0.060) | 0.049 (0.043-0.059) | 0.055 $^{bb}$ (0.048-0.061) | 0.062 $^{a,b}$ (0.046-0.067) | 0.059 $^{a,bb}$ (0.055-0.066) | 0.058 $^{b}$ (0.049-0.074) | <0.001 |
| MPR indeks | 0.038 (0.032-0.048) | 0.038 (0.033-0.047) | 0.041 (0.036-0.048) | 0.045 (0.041-0.047) | 0.046 $^{a,bb,c}$ (0.043-0.052) | 0.039 (0.030-0.056) | 0.008 |

Veći procenat žena bio je uočen u grupi pacijenata sa hipertenzijom (HTA) i kombinacijom dijabetesa (DM) i hipertenzije, kao i u grupi sa dijabetesom i anginom pectoris/AF. Najmlađa grupa bila je sa dijagnozom dijabetesa, dok je najstarija grupa pacijenata bila ona sa hipertenzijom i stentom. Pacijenti sa dijabetesom su imali najviše koncentracije glukoze i HbA1c. Pacijenti sa hipertenzijom su imali najviši ukupni holesterol, kao i LDL-C.

Trigliceridi su bili najviši u grupi sa kombinacijom DM+HTA, ali je HDL-C bio najniži u grupi pacijenata sa DM sa stentom, iako bez statističke značajnosti. Ista grupa je imala najveći NLR indeks, dok je RPR indeks bio najviši kod pacijenata sa HTA+stentom, a MPR indeks je bio najviši u grupi pacijenata sa DM plus stent.

**Tabela 2.** Faktorska analiza u grupi pacijenata sa DM i/ili različitim kardiovaskularnim bolestima

| Faktori | Parametri ekstrahovani u faktore | Opterećenja (engl. *"loadings"*) | Varijabilnost (%) Total: 45% |
|---|---|---|---|
| Starost-hematološki parametri povezan faktor | Erithrociti<br>Hemoglobin<br>Starost (godine) | 0.836<br>0.784<br>-0.611 | 16 |
| Metabolički parameter - bubrežna funkcija povezan faktor | Mokraćna kiselina<br>Trigliceridi<br>Kreatinin | 0.720<br>0.679<br>0.516 | 15 |
| Faktor povezan sa krvnim pritiskom | Dijastolni krvni pritisak<br>Sistolni krvni pritisak | 0.814<br>0.801 | 14 |

## RESULTS

**Table 1.** Baseline clinical and biochemical data of patients with various metabolic and cardiovascular diseases, as well as their combinations (DM, HTN, DM+HTN, HTN + implanted stent, DM + implanted stent, DM + angina pectoris/arrhythmia)

| Parametri | DM (n=52) | DM+HTA (n=139) | HTA (n=55) | HTA+stent (n=11) | DM+stent (n=19) | DM+AP/AF (n=29) | P |
|---|---|---|---|---|---|---|---|
| Gender (m/f), n(%) | 31/21 (59.6/40.4) | 64/75 (46.0/54.0) | 16/39 (29.1/70.9) | 6/5 (54.5/45.5) | 15/4 (78.9/21.1) | 11/18 (37.9/62.1) | 19.7, 0.003 |
| Age (years) | 58 (46-66) | 68 (62-72)$^{aaa}$ | 68 (62-74)$^{aaa}$ | 72 (66-79)$^{aa}$ | 68 (61-73)$^{aa}$ | 68 (64-74)$^{aaa}$ | <0.001 |
| BMI ($kg/m^2$) | 26.7 (24.0-29.5) | 28.6$^{aa}$ (26.1-31.9) | 27.5 (25.1-31.9) | 28.2 (25.7-31.6) | 27.8 (25.2-30.8) | 29.5 (26.9-32.6) | 0.080 |
| Systolic pressure (mm Hg) | 129 (125-132) | 135 (130-140)$^{aaa}$ | 135 (130-145)$^{aa}$ | 130 (130-138) | 130 $^{b,c}$ (120-135) | 130 (120-145) | 0.001 |
| Diastolic pressure (mm Hg) | 82 (80-85) | 83 (80-86) | 84 (78-86) | 85 (75-88) | 80 (70-85) | 80 (75-85) | 0.536 |
| Smoking, no/yes, (%) | 46/6 (18.6/10.3) | 110/29 (44.5/50.0) | 41/14 16.6/24.1) | 10/1 (4.0/1.7) | 16/3 (6.5/5.2) | 24/5 (9.7/8.6) | 4.9, 0.560 |
| Sugar (mmol/L) | 6.6 (5.5-8.8) | 6.8 (5.6-8.4) | 5.5 $^{aaa,bbb}$ (4.9-5.7) | 4.9 $^{aa,bbb}$ (4.8-5.3) | 6.7 $^{ccc,ddd}$ (6.4-7.3) | 6.4 $^{ccc,ddd}$ (5.3-8.0) | <0.001 |
| HbA1c (%) | 7.1 (6.2-7.9) | 6.5 (6.1-7.5) | 5.8 $^{aaa,bbb}$ (5.7-5.9) | 6.2 $^{c}$ (6.1-6.3) | 6.4 $^{ccc}$ (6.2-8.0) | 6.4 $^{cc}$ (5.9-7.0) | <0.001 |
| Cholesterol, total (mmol/L) | 5.07 (4.39-5.76) | 5.09 (4.28-5.97) | 5.72 $^{a,b}$ (4.92-6.12) | 5.39 (4.65-5.97) | 4.60 $^{c}$ (4.15-5.65) | 4.88 $^{cc}$ (4.36-5.40) | 0.047 |
| LDL-C (mmol/L) | 2.86 (2.30-3.72) | 2.71 (2.15-3.53) | 3.55 $^{aa,bbb}$ (2.88-3.90) | 2.48 (2.34-3.31) | 2.46 $^{cc}$ (1.96-2.73) | 2.68 $^{cc}$ (2.03-3.18) | 0.001 |
| HDL-C (mmol/L) | 1.25 (1.03-1.56) | 1.25 (1.06-1.51) | 1.42 $^{b}$ (1.16-1.66) | 1.36 (1.28-1.90) | 1.19 (1.05-1.39) | 1.33 (1.19-1.68) | 0.112 |
| Triglycerides (mmol/L) | 1.54 (1.06-2.38) | 1.90 $^{a}$ (1.40-2.67) | 1.53 $^{bbb}$ (1.21-1.87) | 1.67 (1.15-2.50) | 1.65 (1.18-3.33) | 1.57 $^{bb}$ (1.05-2.10) | 0.003 |
| RPR index | 0.051 (0.044-0.060) | 0.049 (0.043-0.059) | 0.055 $^{bb}$ (0.048-0.061) | 0.062 $^{a,b}$ (0.046-0.067) | 0.059 $^{a,bb}$ (0.055-0.066) | 0.058 $^{b}$ (0.049-0.074) | <0.001 |
| MPR index | 0.038 (0.032-0.048) | 0.038 (0.033-0.047) | 0.041 (0.036-0.048) | 0.045 (0.041-0.047) | 0.046 $^{a,bb,c}$ (0.043-0.052) | 0.039 (0.030-0.056) | 0.008 |

A higher proportion of women was observed in the groups of patients with hypertension (HTN) and the combination of diabetes (DM) and hypertension, as well as in the group with diabetes and angina pectoris/AF. The youngest group consisted of patients diagnosed with diabetes, while the oldest group comprised patients with hypertension and an implanted stent. Patients with diabetes had the highest glucose and HbA1c concentrations. Patients with hypertension exhibited the highest total cholesterol and LDL-C levels.

Triglycerides were highest in the DM+HTN group, whereas HDL-C was lowest in the group of patients with DM and a stent, although this was not statistically significant. The same group had the highest NLR index, while the RPR index was highest in patients with HTN+stent, and the MPR index was highest in the group of patients with DM plus stent..

**Table 2.** Factor analysis in the group of patients with DM and/or various cardiovascular diseases

| Factors | Parameters extracted into factors | loadings | Variability (%) Total: 45% |
|---|---|---|---|
| Age-hematological parameters related factor | Erythrocytes<br>Hemoglobin<br>Age (years) | 0.836<br>0.784<br>-0.611 | 16 |
| Metabolic parameter - renal function related factor | Uric acid<br>Triglycerides<br>Creatinine | 0.720<br>0.679<br>0.516 | 15 |
| A factor associated with blood pressure | Diastolic blood pressure<br>Systolic blood pressure | 0.814<br>0.801 | 14 |

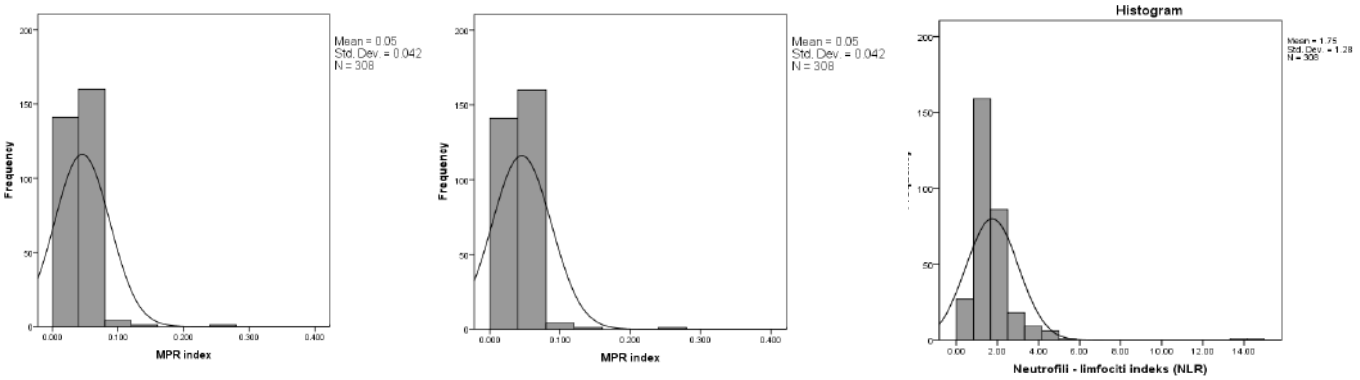
Od svih izmerenih parametara u ovoj studiji primenjena faktorska analiza je proizvela 3 glavna faktora. Prvi faktor pod nazivom „Starost-hematološki parametric povezan faktor" sastojao se od broja eritrocita, koncentracije hemoglobina i starosti (godine) i ovaj faktor je obuhvatio 16% varijabilnosti. Drugi faktor „Faktor vezan za metaboličko-renalnu funkciju" se sastoji od mokraćne kiseline, kreatinina i triglicerida i objašnjava 15% varijabilnosti, dok „Faktor povezan sa krvnim pritiskom" sa 14% varijabilnosti čini sistolni i dijastolni krvni pritisak. Odnos između faktorskom analizom ekstrahovanih faktora i statusa metaboličke/kardiovaskularne bolesti smo proverili korišćenjem logističke regresione analize.

**Tabela 3.** Logistička regresiona analiza prediktora izdvojenih u faktorskoj analizi u vidu skorova (kontinuiranih veličina) za DM, KVB ili njihove kombinacije

| | **Diabetes mellitus (DM) Broj** | | | | **KVB** | | | | **DM+KVB** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Faktori | B (SE) | Wald koef. | OR (95% CI) | P | B (SE) | Wald koef. | OR (95% CI) | P | B (SE) | Wald koef. | OR (95% CI) | P |
| Starost-hematološki parametri povezan faktor | 1.015 (0.607) | 2.80 | feb.76 (0.840-9.06) | 0.094 | -1.18 (0.450) | 6.94 | 0.306 (0.127-0.738) | 0.008 | 0.657 (0.365) | 3.23 | 1.93 (0.942-3.94) | 0.072 |
| Metabolički parameter - bubrežna funkcija povezan faktor | -0.490 (0.669) | 0.53 | 0.613 (0.165-2.274) | 0.464 | -0.464 (0.341) | 1.85 | 0.629 (0.322-1.23) | 0.173 | 0.570 (0.341) | 2.80 | 1.77 (0.908-3.45) | 0.094 |
| Faktor povezan sa krvnim pritiskom | -0.312 (0.440) | 0.50 | 0.732 (0.309-1.73) | 0.477 | -0.012 (0.224) | 0.003 | 0.988 (0.637-1.53) | 0.958 | 0.091 (0.219) | 0.173 | 01.t (0.713-1.68) | 0.677 |

Indeksi aktivacije trombocita (MPR) i eritrocita (RPR) su bili jedan od bitnih delova ovog istraživanja sa ciljem detekcije povećane prokoagulabilnosti u krvi pacijenata iz rutinskih parametara koji se određuju u okviru kompletne krvne slike. Distribucija vrednosti ova dva nova parametra prikazane su na slici 1, kao i raspodela neutrofili limfociti indeksa (NLR, engl. *neutrophil lymphocyte ratio*)

**Slika 1.** Distribucija RPR (A), MPR (B) i NLR (C) vrednosti u grupi pacijenata obolelih od DM i KVB



Of all the measured parameters in this study, factor analysis produced three main factors. The first factor, named the "Age-Hematological Parameter Related Factor," consisted of the number of erythrocytes, hemoglobin concentration, and age (years), and accounted for 16% of the variability. The second factor, the "Metabolic-Renal Function Related Factor," included uric acid, creatinine, and triglycerides, explaining 15% of the variability. The third factor, the "Blood Pressure Related Factor," comprised systolic and diastolic blood pressure and accounted for 14% of the variability. The relationship between the factors extracted by factor analysis and the status of metabolic/cardiovascular disease was assessed using logistic regression analysis..

**Table 3.** Logistic regression analysis of the predictors extracted through factor analysis, expressed as factor scores (continuous variables), was performed for DM, CVD, or their combinations.

| | **Diabetes mellitus (DM) Number** | | | | **CVD** | | | | **DM+ CVD** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Factors | B (SE) | Wald koef. | OR (95% CI) | P | B (SE) | Wald koef. | OR (95% CI) | P | B (SE) | Wald koef. | OR (95% CI) | P |
| Age-hematological parameters related factor | 1.015 (0.607) | 2.80 | feb.76 (0.840-9.06) | 0.094 | -1.18 (0.450) | 6.94 | 0.306 (0.127-0.738) | 0.008 | 0.657 (0.365) | 3.23 | 1.93 (0.942-3.94) | 0.072 |
| Metabolic parameter - renal function related factor | -0.490 (0.669) | 0.53 | 0.613 (0.165-2.274) | 0.464 | -0.464 (0.341) | 1.85 | 0.629 (0.322-1.23) | 0.173 | 0.570 (0.341) | 2.80 | 1.77 (0.908-3.45) | 0.094 |
| A factor associated with blood pressure | -0.312 (0.440) | 0.50 | 0.732 (0.309-1.73) | 0.477 | -0.012 (0.224) | 0.003 | 0.988 (0.637-1.53) | 0.958 | 0.091 (0.219) | 0.173 | 01.t (0.713-1.68) | 0.677 |

Platelet activation (MPR) and erythrocyte activation (RPR) indices were an important part of this study, aimed at detecting increased blood coagulability in patients using routine parameters obtained from a complete blood count. The distribution of values for these two novel parameters is shown in Figure 1, along with the distribution of the neutrophil-to-lymphocyte ratio (NLR)..

**Figure 1.** Distribution of RPR (A), MPR (B), and NLR (C) values in the group of patients with DM and CVD

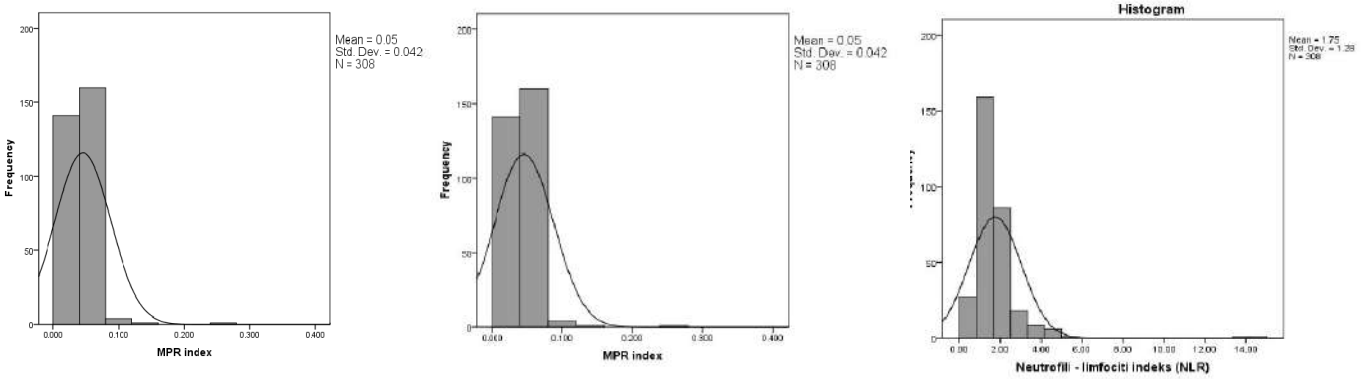


**Tabela 4.** Multipla linearna regresiona analiza prediktora MPR, RPR i NLR vrednosti

| **Model za MPR** | **B (95% CI)** | **SE** | **P** |
|---|---|---|---|
| Aritmija/AF | 0.010 (0.002-0.017) | 0.004 | 0.015 |
| Stent | 0.011 (0.002-0.020) | 0.004 | 0.015 |
| BMI (kg/m2) | -0.001 (-0.001-0.000) | 0.000 | 0.011 |
| Sistolni krvni pritisak (mmHg) | 0.000 (0.000-0.000) | 0.000 | 0.064 |
| Kreatinin (μmol/L) | 0.000 (0.000-0.000) | 0.000 | 0.002 |
| **Model za RPR** | **B (95% CI)** | **SE** | **P** |
| BMI (kg/m2) | -0.001 (-0.001-0.000) | 0.000 | 0.005 |
| Kreatinine (μmol/L) | 0.000 (0.000-0.000) | 0.000 | 0.009 |
| AST (U/L) | 0.000 (0.000-0.001) | 0.000 | 0.088 |
| Model za NLR | B (95% CI) | SE | P |
| Hgb (g/L) | 0.015 (0.002-0.028) | 0.006 | 0.027 |

CI- interval pouzdanosti (engl. confindence interval), SE – standardna greška

Primenjena je multipla linearna regresiona analiza sa ciljem pronalaženja modela značajnih prediktora vrednosti RPR i MPR indeksa. Svi mereni parametri i klinički podaci su uključeni u analizu, a dobijeni rezultati su prikazani u Tabeli 4. MPR vrednost je određena modelom koji se sastoji od prisustva aritmije (atrijalne fibrilacije - AF), indeksa telesne mase (BMI), sistoličkog krvnog pritiska (SBP) i nivoa kreatinina (adjusted $R^2$=0,165). RPR indeks je određen modelom koji se sastoji od prisustva ugrađenog stenta, BMI, koncentracije kreatinina i aspartat aminotransferaze (AST) (adjusted $R^2$=0,145)Iz vrednosti adjusted R2 možemo da zaključimo da odabrani najbolji model prediktora za MPR određuje varijabilnost od oko 16,5% ovog parametra, dok je vrednost RPR parametra određena najboljim modelom koji objašnjava oko 14,5% varijabilnosti ovog parametra. Vrednost NLR parametra je određena modelom u kome je bio samo jedan parametar: hemoglobin (adjusted R2= 0,055), što znači da ovaj model objašnjava 5,5% varijacije u vrijednosti ovog parametra.

## DISKUSIJA

Rezultati ove studije pokazuju da postoje značajne razlike u parametrima kao što su BMI, glukoza, HbA1c, krvni pritisak i lipidi među različitim grupama pacijenata. Ove razlike ukazuju na potrebu za individualizovanim pristupom u proceni i lečenju pacijenata sa kardiovaskularnim bolestima. Uočene varijacije naglašavaju važnost redovnog praćenja ovih ključnih parametara kako bi se pravovremeno identifikovali pacijenti sa povećanim rizikom od komplikacija.

U ovoj studiji učestvovalo je ukupno 311 ispitanika, od kojih je više od polovine ispitanika (59,6%) bilo ženskog pola. Prosečna starost ispitanika bila je 58 godina. Uzorak ispitanika je izabran retrospektivno analizom elektronskih zdravstvenih kartona pacijenata koji su ispunjavali određene kriterijume, a odabir uzorka je izvršen konsekutivnim izborom. U prospektivnom delu studije pratili smo kliničke i laboratorijske parametre tokom svake posete pacijenata.

Analiza kliničkih i laboratorijskih parametara kod pacijenata sa KVB i metaboličkim bolestima otkriva ključne biomarkere koji pružaju važne informacije o stanju pacijenata. BMI, glukoza, HbA1c, ukupni holesterol, LDL-C, HDL-C i trigliceridi su od suštinskog značaja za razumijevanje patofiziologije i rizika povezanih sa različitim zdravstvenim stanjima. BMI je pouzdan pokazatelj telesne mase u odnosu na visinu i često je povezan sa rizikom od razvoja kardiovaskularnih i metaboličkih poremećaja [16].

Nivoi glukoze u krvi i HbA1c predstavljaju ključne indikatore za kontrolu DM, kao i indeks gluzne bvarijabilnosti dok ukupni holesterol i njegove frakcije, kao što su LDL-C i HDL-C, procenjuju lipidni status pacijenta [23]. Studija Artha i saradnika takođe je istraživala odnos između lipidnih profila, lipidnih odnosa i kontrole glikemije kod pacijenata s DMT 2. Studija je pokazala da viši nivoi ukupnog holesterola, lipoproteina niske gustine, triglicerida i lipidnih odnosa koreliraju sa lošijom kontrolom glikemije, što je indikativno kroz više nivoe HbA1c [23]. Nasuprot tome, studija Kidwai i saradnika zapaža da su nivoi lipoproteina visoke gustine niži kod pacijenata

**Table 4.** Multiple linear regression analysis of predictors for MPR, RPR, and NLR values

| **Model for MPR** | **B (95% CI)** | **SE** | **P** |
|---|---|---|---|
| Arrhythmia/AF | 0.010 (0.002-0.017) | 0.004 | 0.015 |
| Stent | 0.011 (0.002-0.020) | 0.004 | 0.015 |
| BMI (kg/m2) | -0.001 (-0.001-0.000) | 0.000 | 0.011 |
| Systolic blood pressure (mmHg) | 0.000 (0.000-0.000) | 0.000 | 0.064 |
| Creatinine (μmol/L) | 0.000 (0.000-0.000) | 0.000 | 0.002 |
| **Model for RPR** | **B (95% CI)** | **SE** | **P** |
| BMI (kg/m2) | -0.001 (-0.001-0.000) | 0.000 | 0.005 |
| Creatinine (μmol/L) | 0.000 (0.000-0.000) | 0.000 | 0.009 |
| AST (U/L) | 0.000 (0.000-0.001) | 0.000 | 0.088 |
| Model for NLR | B (95% CI) | SE | P |
| Hgb (g/L) | 0.015 (0.002-0.028) | 0.006 | 0.027 |

CI- confindence interval, SE – standard error

A multiple linear regression analysis was applied to identify models of significant predictors for the RPR and MPR indices. All measured parameters and clinical data were included in the analysis, and the results are presented in Table 4.

The MPR value was determined by a model consisting of the presence of arrhythmia (atrial fibrillation – AF), body mass index (BMI), systolic blood pressure (SBP), and creatinine levels (adjusted $R^2 = 0.165$). The RPR index was determined by a model including the presence of a coronary stent, BMI, creatinine concentration, and aspartate aminotransferase (AST) (adjusted $R^2 = 0.145$).

From the adjusted $R^2$ values, it can be concluded that the selected best model of predictors for MPR explains approximately 16.5% of the variability of this parameter, while the RPR parameter variability is explained by the best model at about 14.5%. The NLR value was determined by a model including only one parameter, hemoglobin (adjusted $R^2 = 0.055$), indicating that this model explains 5.5% of the variation in NLR..

## DISCUSSION

The results of this study show significant differences in parameters such as BMI, glucose, HbA1c, blood pressure, and lipids among different groups of patients. These differences highlight the need for an individualized approach in the assessment and management of patients with cardiovascular diseases. The observed variations emphasize the importance of regular monitoring of these key parameters to timely identify patients at increased risk of complications.

A total of 311 participants were included in the study, with more than half (59.6%) being female. The average age of participants was 58 years. The sample was retrospectively selected through an analysis of patients' electronic health records who met specific criteria, with a consecutive sampling method. In the prospective part of the study, clinical and laboratory parameters were monitored during each patient visit.

Analysis of clinical and laboratory parameters in patients with cardiovascular and metabolic diseases revealed key biomarkers that provide valuable information about the patients' condition. BMI, glucose, HbA1c, total cholesterol, LDL-C, HDL-C, and triglycerides are essential for understanding the pathophysiology and risk associated with different health conditions. BMI is a reliable indicator of body mass relative to height and is often associated with the risk of developing cardiovascular and metabolic disorders [16].

Blood glucose levels and HbA1c are key indicators for diabetes management, reflecting glycemic control and variability, while total cholesterol and its fractions, such as LDL-C and HDL-C, assess the patient's lipid status [23]. The study by Artha et al. also examined the relationship between lipid profiles, lipid ratios, and glycemic control in patients with type 2 diabetes. It showed that higher levels of total cholesterol, low-density lipoprotein, triglycerides, and lipid ratios correlate with poorer glycemic control, as indicated by higher

sa lošijom kontrolom glikemije [24]. Shodno tome, pomenuta studija indentifikuje ratio LDL-C/HDL-C kao značajan faktor rizika za lošu kontrolu glikemije, pri čemu visok odnos povećava rizik 38 puta. Ipak, važno je napomenuti da, iako je ovaj odnos koristan u teorijskoj proceni, u praksi se često ističe prognostički značaj lipoproteina (Lp(a)), apolipoproteina A (apo A) i apolipoproteina B (apo B), kao i prisustvo malih gustih LDL čestica, koji mogu imati značajniju ulogu u proceni rizika i upravljanju kardiovaskularnim bolestima. Ovi nalazi sugerišu da lipidni profili i odnosi mogu služiti kao prediktivni markeri za kontrolu glikemije, što može pomoći u upravljanju kardiovaskularnim rizikom kod pacijenata s dijabetesom. Takođe, značajno je naglašena važnost praćenja nivoa lipida uz kontrolu glikemije kako bi se smanjili kardiovaskularne komplikacije povezane sa DM.

Povišeni nivoi triglicerida mogu biti indikatori metaboličkog sindroma i povezani su sa povećanim rizikom od KBS [23]. Analizom osnovnih kliničkih i biohemijskih podataka uočili smo da su pacijenti sa DM pokazali značajno veći BMI, nivoe glukoze, HbA1c i HDL-C u poređenju sa gornjom granicom referentnih vrednosti, dok je njihov dijastolni pritisak bio znatno niži od te granice. Shodno navedenom, u našoj studiji BMI, glukoza i HbA1c su pokazali značajne varijacije među pacijentima sa DM, HTA i njihovim kombinacijama. Ovi parametri su ključni indikatori metaboličkog zdravlja i njihova kontrola je od suštinskog značaja za smanjenje rizika od komplikacija. Takođe, razlike u nivou sistolnog i dijastolnog pritiska među grupama dodatno osvetljavaju njihov doprinos kardiovaskularnom riziku, posebno kod pacijenata sa HTA i ugrađenim stentom.

U studiji Brittona i saradnika istraživana je korelacija između nivoa hemoglobina A1c (HbA1c), indeksa telesne mase (BMI) i rizika od razvoja hipertenzije (HTA). Cilj studije bio je utvrditi da li postoji prospektivna povezanost između početnih vrednosti HbA1c i incidencije HTA tokom vremena, uzimajući u obzir i ulogu telesne težine. Ova studija je od posebnog značaja, jer povišeni HbA1c može ukazivati na lošu kontrolu šećera u krvi, što je faktor rizika za razvoj hipertenzije, a BMI je poznati pokazatelj telesne mase koji takođe može uticati na kardiovaskularno zdravlje. Zaključci autora su u skladu s nalazima naše studije [26]. Brittonova studija ističe važnost BMI, nivoa glukoze i HbA1c kao ključnih indikatora metaboličkog zdravlja. Povišeni BMI može ukazivati na prekomernu telesnu težinu ili gojaznost, što su faktori koji mogu povećati rizik od hipertenzije zbog dodatnog opterećenja na srce i krvne sudove. S druge strane, visoki nivoi HbA1c sugerišu na hroničnu hiperglikemiju, koja može dovesti do oštećenja krvnih sudova i upalnih procesa, dodatno povećavajući rizik od kardiovaskularnih problema. Ove tvrdnje potvrđuju i druge publikovane studije [27,28], što dodatno jača našu hipotezu o povezanosti ovih varijabli i rizika od hipertenzije. Naši nalazi su u skladu sa prethodnim istraživanjima koja su pokazala da su povišeni nivoi HbA1c i BMI povezani sa višim rizikom od hipertenzije. Na primer, neka istraživanja su ukazala na to da čak i blago povišeni nivoi HbA1c mogu biti indikativni za povećan rizik od HTA, dok drugi dokazi sugerišu da intervencije usmerene na smanjenje BMI mogu smanjiti incidenciju hipertenzije kod pacijenata sa metaboličkim sindromom. Ovi rezultati ukazuju na to da bi upravljanje težinom i kontrola glikemije mogli biti ključni elementi u prevenciji hipertenzije, što se takođe oslanja na nalaze naše studije. Dodatno, Izraelska studija iz 2021. godine [29] pruža dodatne dokaze o tome da povišeni nivoi HbA1c i BMI značajno doprinose razvoju hipertenzije. Ovi rezultati naglašavaju potrebu za redovnim praćenjem metaboličkih faktora kao što su HbA1c i BMI, posebno kod pacijenata sa povećanim rizikom od kardiovaskularnih bolesti. Uzimajući u obzir sve navedeno, jasno je da su HbA1c i BMI ključni pokazatelji zdravlja koji mogu značajno uticati na rizik od hipertenzije. Rezultati pomenute studije pokazuju da varijabilnost hemoglobina A1c (HbA1c) predstavlja nezavisni faktor rizika za komplikacije povezane sa dijabetesom (DM). U ovoj studiji, otkriveno je da je oko 22% ispitanika imalo visoku varijabilnost HbA1c, što je bilo povezano sa višim indeksom telesne mase (BMI) od 30 ili više. Ova povezanost sugeriše da pacijenti sa višim BMI često imaju manje stabilne nivoe šećera u krvi, što može povećati rizik od komplikacija poput kardiovaskularnih bolesti i neuropatije. Dodatno, ispitanici sa visokom varijabilnošću HbA1c su imali češće posete klinikama za dijabetes, što može ukazivati na složeniji profil bolesti i potrebu za intenzivnijim nadzorom i lečenjem. Ovi pacijenti su često koristili insulin i ACE inhibitore, a njihova starost, kao i prisustvo ishemijske bolesti srca, takođe su bili značajni faktori.

HbA1c levels [23]. In contrast, the study by Kidwai et al. observed that high-density lipoprotein levels were lower in patients with poor glycemic control [24].

Accordingly, the LDL-C/HDL-C ratio has been identified as a significant risk factor for poor glycemic control, with a high ratio increasing the risk 38-fold. However, it is important to note that while this ratio is useful in theoretical assessment, in practice, the prognostic value of lipoproteins (Lp(a)), apolipoprotein A (apo A), apolipoprotein B (apo B), and the presence of small dense LDL particles may play a more significant role in risk assessment and cardiovascular disease management. These findings suggest that lipid profiles and ratios can serve as predictive markers for glycemic control, helping to manage cardiovascular risk in patients with diabetes. Additionally, regular monitoring of lipid levels alongside glycemic control is emphasized as crucial for reducing diabetes-related cardiovascular complications..

levated triglyceride levels can be indicators of metabolic syndrome and are associated with an increased risk of coronary artery disease (CAD) [23]. Analysis of basic clinical and biochemical data revealed that patients with diabetes (DM) had significantly higher BMI, glucose, HbA1c, and HDL-C levels compared to the upper limit of reference values, while their diastolic blood pressure was significantly lower than this threshold. Accordingly, in our study, BMI, glucose, and HbA1c showed significant variations among patients with DM, hypertension (HTA), and their combinations. These parameters are key indicators of metabolic health, and their control is crucial for reducing the risk of complications. Differences in systolic and diastolic blood pressure among the groups further highlight their contribution to cardiovascular risk, especially in patients with HTA and implanted stents.

The study by Britton et al. investigated the correlation between hemoglobin A1c (HbA1c), body mass index (BMI), and the risk of developing hypertension (HTA). The aim was to determine whether there is a prospective association between baseline HbA1c values and the incidence of HTA over time, considering the role of body weight. This study is particularly important, as elevated HbA1c may indicate poor blood sugar control, a risk factor for developing hypertension, while BMI is a well-known indicator of body mass that can also influence cardiovascular health. The authors' conclusions are consistent with the findings of our study [26]. Britton's study emphasizes the importance of BMI, glucose levels, and HbA1c as key indicators of metabolic health. Elevated BMI may indicate overweight or obesity, factors that can increase hypertension risk due to added strain on the heart and blood vessels. High HbA1c levels suggest chronic hyperglycemia, which can lead to vascular damage and inflammatory processes, further increasing cardiovascular risk. These findings are supported by other published studies [27,28], reinforcing our hypothesis regarding the link between these variables and hypertension risk.

Our findings align with previous research showing that elevated HbA1c and BMI are associated with higher hypertension risk. For example, some studies indicate that even mildly elevated HbA1c levels may be indicative of increased HTA risk, while other evidence suggests that interventions aimed at reducing BMI can lower hypertension incidence in patients with metabolic syndrome. These results suggest that weight management and glycemic control may be key elements in preventing hypertension, which is consistent with our study's findings.

Furthermore, an Israeli study from 2021 [29] provides additional evidence that elevated HbA1c and BMI levels significantly contribute to the development of hypertension. These results underscore the need for regular monitoring of metabolic factors such as HbA1c and BMI, especially in patients at increased cardiovascular risk. Taken together, it is clear that HbA1c and BMI are key health indicators that can significantly influence hypertension risk.

The results of that study also showed that HbA1c variability is an independent risk factor for diabetes-related complications. Approximately 22% of participants had high HbA1c variability, which was associated with a BMI of 30 or higher. This suggests that patients with higher BMI often have less stable blood sugar levels, increasing the risk of complications such as cardiovascular disease and neuropathy.

Povezanost između visoke varijabilnosti HbA1c i mladih godina, kao i visokog BMI, može sugerisati da se rizični faktori za komplikacije često javljaju zajedno, stvarajući složeniji obrazac upravljanja dijabetesom. Ovi nalazi ukazuju na to da varijabilnost HbA1c može poslužiti kao marker složenosti bolesti i načina života pacijenata, naglašavajući važnost praćenja fluktuacija nivoa HbA1c. Ova studija podržava zapažanja naše studije o značaju BMI, glukoze i HbA1c kao ključnih indikatora metaboličkog zdravlja. Takođe, naglašava se njihova uloga u smanjenju rizika od komplikacija kod pacijenata sa dijabetesom i hipertenzijom. U svetlu ovih nalaza, važno je dodatno razmotriti uticaj varijabilnosti HbA1c na kliničku praksu. Praćenje i analiza ovih fluktuacija mogu pomoći lekarima da bolje razumeju dinamiku bolesti kod pacijenata i identifikuju one koji su u većem riziku od razvoja ozbiljnih komplikacija. Implementacija strategija za upravljanje težinom i kontrolu glikemije može biti ključna u prevenciji hipertenzije i drugih kardiovaskularnih problema, čime se dodatno potkrepljuju naši nalazi.

Indeksi kao što su MPR, RPR i NLR pokazali su se korisnim u proceni prokoagulabilnosti i inflamatornog statusa, pružajući važne informacije o zdravstvenom stanju pacijenata. Ovi parametri mogu služiti kao rani indikatori povećanog rizika kod pacijenata sa složenim komorbiditetima, omogućavajući pravovremenu intervenciju i prilagođavanje terapijskih strategija. MPR, odnosno monocitno-plateletni odnos, može ukazivati na promene u imunološkom i koagulacionom sistemu. RPR, odnos retikulocita prema trombocitima, pomaže u proceni regenerativnog kapaciteta koštane srži i koagulacione aktivnosti. NLR, odnos neutrofila prema limfocitima je jednostavan ali efikasan marker inflamacije i stresa. Korišćenjem ovih indeksa, kliničari mogu bolje razumeti i upravljati rizicima kod pacijenata, što može poboljšati ishode lečenja i prilagoditi terapijske planove u skladu sa specifičnim potrebama pacijenta. Dakle, ovi parametri mogu služiti kao rani indikatori povećanog rizika kod pacijenata sa složenim komorbiditetima, omogućavajući pravovremenu intervenciju i prilagođavanje terapijskih strategija. Rezultati naše studije pružaju značajne uvide u ulogu indeksa kao što su MPR, RPR i NLR. Rezultati naše studije pokazuju da su vrednosti MPR indeksa najviše kod pacijenata sa DM i ugrađenim stentom. Ovaj indeks može biti posebno koristan u proceni rizika od tromboze, jer ukazuje na aktivaciju trombocita, što je često povezano sa povećanom prokoagulabilnošću krvi. U našem istraživanju, prisustvo ugrađenog stenta i faktori poput AF i aritmije su identifikovani kao značajni prediktori vrijednosti MPR, što može ukazivati na veću sklonost ka trombotskim događajima kod ovih pacijenata. Dalje, rezultati pokazuju da je RPR indeks najviši kod pacijenata sa HTA i ugrađenim stentom. Ovaj indeks može ukazivati na promene u hematopoetskom sistemu i može biti koristan u proceni koagulacionog statusa. Rezultati naše studije ukazali su da prisustvo stenta, BMI i koncentracija kreatinina značajno utiču na vrednosti RPR, što je od posebnog značaja za identifikaciju pacijenata sa potencijalno povećanim rizikom od komplikacija povezanih sa koagulacijom.

Iako nije dominantan u našem modelu studije, NLR (odnos neutrofila i limfocita) prepoznat je kao značajan marker inflamacije. Naše istraživanje naglašava da NLR može poslužiti kao koristan alat za ranu identifikaciju pacijenata sa povećanim rizikom od komplikacija. Ova identifikacija omogućava kliničarima da prilagode terapijske strategije i poboljšaju ishode lečenja. Kada se NLR analizira zajedno sa drugim kliničkim i laboratorijskim parametrima, može doprineti preciznijem praćenju i upravljanju pacijentima sa složenim komorbiditetima. U literaturi se takođe ističe značaj drugih inflamatornih markera, kao što je hsCRP (high-sensitivity C-reactive protein), koji se često koristi za procenu inflamatornog stanja i rizika od kardiovaskularnih bolesti. Istraživanja su pokazala da su povišeni nivoi hsCRP povezani sa povećanim rizikom od komplikacija kod pacijenata sa različitim hroničnim stanjima, uključujući dijabetes i hipertenziju [37,38]. U poređenju sa NLR, hsCRP nudi dodatnu prednost u smislu visoke osetljivosti za detekciju blagih inflamatornih stanja. Dok NLR pruža korisne informacije o ravnoteži između neutrofila i limfocita, što može reflektovati opšte imunološko stanje, hsCRP direktno meri nivo inflamacije u organizmu. Ova komplementarnost između NLR i hsCRP može poboljšati naše razumevanje inflamatornih procesa kod pacijenata sa složenim komorbiditetima. U studijama koje istražuju ulogu inflamatornih markera, kao što su NLR i hsCRP, utvrđeno je da ovi indeksi mogu poslužiti kao rani indikatori povećanog rizika kod pacijenata sa složenim

Additionally, patients with high HbA1c variability had more frequent visits to diabetes clinics, indicating a more complex disease profile requiring intensive monitoring and treatment. These patients often used insulin and ACE inhibitors, and their age as well as the presence of ischemic heart disease were also significant factors. The association between high HbA1c variability, younger age, and high BMI suggests that risk factors for complications often occur together, creating a more complex pattern of diabetes management.

These findings indicate that HbA1c variability can serve as a marker of disease complexity and lifestyle, highlighting the importance of monitoring HbA1c fluctuations. This study supports the observations from our research on the significance of BMI, glucose, and HbA1c as key indicators of metabolic health. It also emphasizes their role in reducing the risk of complications in patients with diabetes and hypertension. In light of these findings, it is important to consider the impact of HbA1c variability on clinical practice. Monitoring and analyzing these fluctuations can help clinicians better understand disease dynamics and identify patients at higher risk of developing serious complications. Implementing strategies for weight management and glycemic control may be crucial in preventing hypertension and other cardiovascular problems, further reinforcing the conclusions of our study..

Indices such as MPR, RPR, and NLR have proven useful in assessing procoagulant activity and inflammatory status, providing important insights into patients' health. These parameters can serve as early indicators of increased risk in patients with complex comorbidities, enabling timely intervention and tailored therapeutic strategies.

MPR, the monocyte-to-platelet ratio, can indicate changes in the immune and coagulation systems. RPR, the reticulocyte-to-platelet ratio, helps assess the regenerative capacity of the bone marrow and coagulation activity. NLR, the neutrophil-to-lymphocyte ratio, is a simple yet effective marker of inflammation and stress. By using these indices, clinicians can better understand and manage patient risks, potentially improving treatment outcomes and adjusting therapeutic plans according to individual patient needs.

Our study results highlight that MPR values were highest in patients with diabetes (DM) and an implanted stent. This index may be particularly useful in assessing thrombotic risk, as it indicates platelet activation, which is often associated with increased blood coagulability. In our research, the presence of a stent and factors such as atrial fibrillation (AF) and other arrhythmias were identified as significant predictors of MPR values, suggesting a higher predisposition to thrombotic events in these patients.

Furthermore, RPR values were highest in patients with hypertension (HTA) and an implanted stent. This index may reflect changes in the hematopoietic system and can be useful in evaluating coagulation status. Our study indicated that the presence of a stent, BMI, and creatinine levels significantly influenced RPR values, which is important for identifying patients potentially at increased risk of coagulation-related complications.

Although less dominant in our model, NLR was recognized as a significant marker of inflammation. Our findings emphasize that NLR can serve as a useful tool for the early identification of patients at higher risk of complications, allowing clinicians to adjust therapeutic strategies and improve outcomes. When analyzed alongside other clinical and laboratory parameters, NLR contributes to more precise monitoring and management of patients with complex comorbidities.

The literature also underscores the importance of other inflammatory markers, such as hsCRP (high-sensitivity C-reactive protein), commonly used to assess inflammatory status and cardiovascular risk. Elevated hsCRP levels have been associated with increased complication risk in patients with chronic conditions, including diabetes and hypertension [37,38]. Compared to NLR, hsCRP offers the advantage of high sensitivity for detecting low-grade inflammation. While NLR provides insight into the balance between neutrophils and lymphocytes, reflecting general immune status, hsCRP directly measures inflammation levels in the body. The complementary nature of NLR and hsCRP enhances understanding of inflammatory processes in patients with complex

komorbiditetima [38]. Uzimajući u obzir njihovu komplementarnu prirodu, kliničari bi mogli razmotriti korišćenje oba markera u rutinskom praćenju i proceni rizika kod pacijenata, čime bi se omogućila pravovremena intervencija i optimizacija terapijskih pristupa. Na primer, studija autora Thurston i saradnika zaključuje da veće vrednosti NLR često reflektuju povećani inflamatorni odgovor, koji je povezan sa kardiovaskularnim rizicima [30]. Navedena studija, baš kao i naša ukazuju na to da ovi markeri mogu služiti kao rani indikatori rizika kod pacijenata sa složenim komorbiditetima, pružajući važne informacije o zdravstvenom stanju i potencijalnim rizicima od kardiovaskularnih komplikacija. Takođe, Li i saradnici su u studiji koja je objavljena početkom novembra 2024. godine, istakli izuzetan značaj odnosa neutrofila prema limfocitima u proceni rizika od KVB [31]. U ovoj studiji, analizirani su podaci od 2.239 učesnika sa KVB i utvrđeno je da više vrednosti NLR-a koreliraju sa povećanim rizikom od smrtnosti, kako od svih uzroka, tako i specifično od kardiovaskularnih uzroka. Studija je koristila podatke iz Nacionalne ankete o zdravlju i ishrani (NHANES) sprovedene između 1999. i 2018. godine, i pokazala je da je viši NLR nezavisno prediktivan za povećan rizik od smrtnosti, čak i nakon prilagođavanja za različite demografske i kliničke faktore. U studiji je utvrđeno da je svako povećanje neutrofila prema limfocitima (NLR) za jedan poen povezano sa 15% višim rizikom od smrtnosti od svih uzroka (HR: 1.15; 95% CI: 1.11–1.19) kao i 14% višim rizikom od kardiovaskularne smrtnosti (HR: 1.14; 95% CI: 1.08–1.20) u modelu koji je uključivao sve relevantne varijable. U analizi podataka, HR za NLR kao kontinualnu varijablu ukazuje na pozitivnu povezanost sa smrtnosti. Za sve uzroke, HR iznosi 1,15, što znači da svako povećanje NLR za 1 dovodi do 15% povećanja rizika od smrtnosti. Slična jačina korelacije primećena je i za kardiovaskularnu smrtnost. P-vrednosti za sve analize su značajne, sa $p<0,001$, što ukazuje na vrlo visoku statističku značajnost u vezi između povišenog NLR i rizika od smrtnosti. Analiza pomoću restriktivnog kubnog splina pokazala je da postoji nelinearna veza između NLR i smrtnosti od svih uzroka ($p<0,05$ za nelinearnost), što ukazuje da povećanje NLR može imati složeniji odnos sa rizikom od smrtnosti, posebno u višim opsezima. Ovi nalazi takođe podržavaju vašu tvrdnju da NLR, kao i drugi inflamatorni indeksi poput MPR i RPR, mogu služiti kao efikasni indikatori za stratifikaciju rizika i procenu prognoze kod pacijenata sa KVB. Studija naglašava potencijal NLR-a da posluži kao troškovno efikasan marker u kliničkim postavkama.

Faktorska analiza je identifikovala „starost-hematološki faktor“ i „metaboličko-bubrežni faktor“ kao značajne varijable povezane sa rizikom. Ovi faktori objedinjuju varijabilnost među kliničkim i biohemijskim parametrima, pružajući dublje razumevanje složenih interakcija koje doprinose kardiovaskularnom riziku. Posebno, faktor povezan sa krvnim pritiskom pokazao je značajan doprinos ukupnoj proceni rizika, što naglašava potrebu za njegovom kontrolom u kliničkoj praksi. Naša studija je identifikovala „starost-hematološki faktor“ koji uključuje broj eritrocita, koncentraciju hemoglobina i starost. Ovaj faktor obuhvata 16% varijabilnosti i pokazuje kako starosne i hematološke karakteristike mogu biti povezane sa povećanim kardiovaskularnim rizikom. Povezanost starosti sa hematološkim parametrima, kao što je anemija, često je u korelaciji sa povećanim rizikom od kardiovaskularnih bolesti, što našu analizu čini relevantnom za procenu celokupnog zdravstvenog stanja pacijenata. Jedna od relevantnih studija koja se bavi starosnim i hematološkim faktorima u kontekstu kardiovaskularnog rizika je studija Truslowa i saradnika. Naime, ovo istraživanje, baš kao i naše, bavi se upotrebom hematoloških markera, dobijenih iz kompletne krvne slike, u razvoju prediktivnih modela za kardiovaskularne događaje [32]. Pomenuta studija je koristila Cox-ove proporcionalne hazard modele za predikciju ishoda kao što su srčani udar, ishemijski moždani udar, hospitalizacija zbog srčane insuficijencije, revaskularizacija i smrtnost iz svih uzroka i metodologija modeliranja se razlikuje od naše u okviru koje smo koristili specifične statističke modele ili indekse, ali rezultati su pokazali da modeli koji uključuju hematološke indekse pružaju bolje predikcije u poređenju sa modelima koji koriste samo demografske podatke i dijagnostičke kodove. Konkretno, modeli su pokazali najbolju performansu u predviđanju srčane insuficijencije i smrtnosti iz svih uzroka, sa indeksima slaganja u rasponu od 0,60 do 0,80. Shodno navedenom, studija Truslowa i saradnika naglašava potencijal korišćenja hematoloških markera, kao što su broj eritrocita i koncentracija hemoglobina, u

comorbidities. Studies investigating inflammatory markers, including NLR and hsCRP, have shown that these indices can serve as early indicators of increased risk in such patients [38]. Considering their complementary roles, clinicians may consider using both markers in routine risk assessment, enabling timely intervention and optimized therapeutic approaches.

For example, Thurston et al. found that higher NLR values often reflect an increased inflammatory response, which is associated with cardiovascular risks [30]. This study, like ours, suggests that these markers can serve as early risk indicators in patients with complex comorbidities, providing important information on health status and potential cardiovascular complications. Additionally, Li et al., in a study published in early November 2024, highlighted the exceptional value of the neutrophil-to-lymphocyte ratio in assessing cardiovascular risk [31]. Analyzing data from 2,239 participants with cardiovascular disease (CVD), they found that higher NLR values correlated with increased risk of all-cause and cardiovascular mortality. Using data from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2018, the study demonstrated that higher NLR independently predicted increased mortality risk, even after adjusting for demographic and clinical factors. Each one-unit increase in NLR was associated with a 15% higher risk of all-cause mortality (HR: 1.15; 95% CI: 1.11–1.19) and a 14% higher risk of cardiovascular mortality (HR: 1.14; 95% CI: 1.08–1.20) in a model including all relevant variables. Restricted cubic spline analysis indicated a nonlinear relationship between NLR and all-cause mortality ($p<0.05$ for nonlinearity), suggesting that increasing NLR may have a more complex relationship with mortality risk, particularly at higher levels. These findings support our conclusion that NLR, like other inflammatory indices such as MPR and RPR, can be effective indicators for risk stratification and prognosis assessment in patients with CVD. The study emphasizes NLR's potential as a cost-effective clinical marker.

Factor analysis identified the "age-hematologic factor" and "metabolic-renal factor" as significant variables related to risk. These factors consolidate variability among clinical and biochemical parameters, providing deeper insight into the complex interactions contributing to cardiovascular risk. Notably, the blood pressure-related factor showed a significant contribution to overall risk assessment, underscoring the need for its management in clinical practice.

Our study identified the "age-hematologic factor," which includes red blood cell count, hemoglobin concentration, and age. This factor accounted for 16% of variability and demonstrates how age and hematologic characteristics may be associated with increased cardiovascular risk. The association of age with hematologic parameters, such as anemia, is often correlated with higher CVD risk, making our analysis relevant for assessing overall patient health.

A relevant study addressing age and hematologic factors in the context of cardiovascular risk is by Truslowa et al. Like our research, it investigated the use of hematologic markers from complete blood counts in developing predictive models for cardiovascular events [32]. That study used Cox proportional hazards models to predict outcomes such as myocardial infarction, ischemic stroke, heart failure hospitalization, revascularization, and all-cause mortality. While the modeling methodology differs from ours, the results showed that models including hematologic indices provide better predictions than models using only demographic data and diagnostic codes. Specifically, models performed best in predicting heart failure and all-cause mortality, with concordance indices ranging from 0.60 to 0.80. Consequently, Truslowa et al. highlight the potential of using hematologic markers, such as red blood cell count and hemoglobin concentration, in assessing cardiovascular risk, supporting our observations regarding the "age-hematologic factor.".

The blood pressure factor consists of systolic and diastolic blood pressure and accounts for 14% of variability. Our study highlights the importance of this factor in overall risk assessment. Hypertension (HTA) is a well-known risk factor for cardiovascular disease (CVD), and blood pressure control is essential to reduce the risk of heart attacks and strokes. These results are consistent with previously published studies examining the correlation

proceni kardiovaskularnog rizika, što podržava naša zapažanja o "starost-hematološkom faktoru".

Faktor krvnog pritiska se sastoji od sistolnog i dijastolnog krvnog pritiska i obuhvata 14% varijabilnosti. Naša studija ističe važnost ovog faktora u ukupnoj proceni rizika. HTA je poznati faktor rizika za KVB, a kontrola pritiska je ključna za smanjenje rizika od srčanih i moždanih udara. Ovakvi rezultati su u skladu sa do sada publikovanim studijama koje su razmatrale korelaciju između HTA i KVB [28,33]. Diskusija o ovom faktoru naglašava njegovu praktičnu primjenu u kliničkim postavkama, gde je monitoring i upravljanje krvnim pritiskom od suštinskog značaja za prevenciju kardiovaskularnih događaja.

Ograničenja ove studije uključuju retrospektivni dizajn i uzorak ograničen na jednu zdravstvenu ustanovu. Buduća istraživanja bi mogla uključivati longitudinalne studije za praćenje dugoročnih ishoda, kao i ispitivanje dodatnih biomarkera koji bi mogli unaprediti procenu rizika kod sličnih pacijenata.

## ZAKLJUČAK

Rezultati ove studije ukazuju da inflamatorno-hemostatski indeksi, poput MPR i RPR, zajedno sa kliničkim faktorima, predstavljaju korisne alate za procenu rizika kod pacijenata sa kardiovaskularnim bolestima. Najveće vrednosti MPR indeksa zabeležene su kod pacijenata sa dijabetesom i ugrađenim stentom, dok je najviši RPR indeks utvrđen kod pacijenata sa hipertenzijom i stentom, što sugeriše prisustvo izraženog inflamatornog i prokoagulantnog statusa u ovim podgrupama.

Faktorska analiza je dodatno potvrdila značaj starosno-hematološkog klastera kao jedinog nezavisnog prediktora prisustva kardiovaskularnih bolesti. Ovi nalazi podvlače značaj integracije jednostavnih, rutinski dostupnih hematoloških pokazatelja sa kliničkim podacima u cilju rane identifikacije visokorizičnih pacijenata.

Uvođenje ovih parametara u svakodnevnu kliničku praksu može unaprediti dijagnostiku, omogućiti personalizovanu terapiju i doprineti efikasnijoj primarnoj i sekundarnoj prevenciji kardiovaskularnih bolesti.

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between HTA and CVD [28,33]. The discussion of this factor emphasizes its practical application in clinical settings, where monitoring and managing blood pressure is crucial for preventing cardiovascular events.

Limitations of this study include its retrospective design and a sample restricted to a single healthcare institution. Future research could include longitudinal studies to track long-term outcomes, as well as investigation of additional biomarkers that may improve risk assessment in similar patient populations..

## CONCLUSION

The results of this study indicate that inflammatory-hemostatic indices, such as MPR and RPR, together with clinical factors, serve as useful tools for risk assessment in patients with cardiovascular diseases. The highest MPR values were observed in patients with diabetes and an implanted stent, while the highest RPR values were found in patients with hypertension and a stent, suggesting a pronounced inflammatory and procoagulant status in these subgroups.

Factor analysis further confirmed the significance of the age-hematological cluster as the sole independent predictor of the presence of cardiovascular disease. These findings underscore the importance of integrating simple, routinely available hematological markers with clinical data to enable early identification of high-risk patients.

Incorporating these parameters into daily clinical practice may enhance diagnostics, allow for personalized therapy, and contribute to more effective primary and secondary prevention of cardiovascular diseases..

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# LAJMSKA BOLEST

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**Sažetak:** Lajmska bolest (Lb) je multisistemska infektivna bolest izazvana bakterijama roda Borrelia, najčešće Borrelia burgdorferi, a prenosi je ubod zaraženog krpelja Ixodes ricinus. Glodari (miševi, pacovi) su primarni rezervoari bakterija. Prenos bakterija je najčešći u periodu od maja do avgusta u umerenim klimatskim zonama, ali bolest može da se javi i van ovog perioda, zavisno od klimatskih uslova i aktivnosti krpelja. U ranoj fazi, Lajmska bolest se najčešće manifestuje pojavom karakteristične lezije na koži, poznate kao erythema migrans, koja počinje kao crvena makula ili papula i može se proširiti do 50 cm, sa centralnim prosvetljenjem i jasno ili blago definisanim rubovima. Pored toga, simptomi mogu uključivati glavobolju, povišenu temperaturu, malaksalost, bolove u mišićima i zglobovima, što može dovesti do pogrešne dijagnoze ili odlaganja terapije. Ako se bolest ne leči na vreme, može izazvati ozbiljne sistemske komplikacije, uključujući neurološke poremećaje (npr. meningitis, neuropatije), srčane probleme (atrioventrikularni blok) i artritis, najčešće zahvatajući kolena. Kasni stadijumi bolesti mogu trajati mesecima ili godinama, ali adekvatnom antibiotskom terapijom simptomi se često mogu smanjiti. Dijagnostika se zasniva na kliničkoj slici i serološkim testovima, kao što su ELISA i Western blot, koji detektuju prisustvo antitela na bakterije. Važno je napomenuti da serološki testovi u ranoj fazi mogu biti negativni, jer antitela još nisu razvijena. PCR testovi mogu potvrditi prisustvo bakterija direktnim ispitivanjem uzoraka krvi, likvora ili tkiva, ali se u rutinskoj dijagnostici erythema migrans kao klinička dijagnoza smatra dovoljnim razlogom za započinjanje terapije. Prevencija se zasniva na smanjenju kontakta sa krpeljima, uključujući nošenje adekvatne zaštitne odeće, primenu repelenata, tretiranje odeće permetrinom. U preventivne mere spada košenje i održavanje travnatih površina, kao i kontrola populacije glodara i krpelja na mestima gde ljudi borave.
**Ključne reči**: Lajmska bolest, Borrelia burgdorferi, Ixodes ricinus, vektorska infekcija, erythema migrans, prenos bakterije, dijagnostika, serološki testovi, prevencija, komplikacije, artritis, neurološki poremećaji, krpelj i glodari

## DEFINICIJA I EPIDEMIOLOGIJA LAJMSKE BOLESTI

Lajmska bolest (Lb) ili MORBUS LYME je hronično multisistemsko infektivno oboljenje koje kod čoveka nastaje ubodom zaraženog tvrdog krpelja Ixodes ricinus, zaraženog jednom od bakterija kao što su *Borrelia burgdorferi (Bb)* (Slika 1), i ređe druge Borrelia vrste: *Borrelia garinii (Bg) i Borrelia afzelii (Ba).* To je multisistemska bolest koja može da pogodi kožu, zglobove, srce i nervni sistem. Poznata je po tome što se često manifestuje karakterističnim znakom "migrirajućeg eritema" (crvenilo u obliku mete) [1].

**Slika 1.** *Borrelia burgdorferi* uvećana 400 puta
preuzeto sa: https://upload.wikimedia.org/wikipedia/commons/f/f3/Borrelia_burgdorferi_%28CDC-PHIL_-6631%29_lores.jpg


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# LYME DISEASE

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**Summary:** Lyme disease (LD) is a multisystem infectious disease caused by bacteria of the Borrelia genus, most commonly Borrelia burgdorferi, and transmitted through the bite of an infected tick (Ixodes ricinus). Rodents (mice, rats) are the primary reservoirs of the bacteria. Transmission occurs most frequently between May and August in temperate climate zones, although the disease can appear outside this period depending on climatic conditions and tick activity. In its early stage, Lyme disease most commonly manifests as a characteristic skin lesion known as erythema migrans, which begins as a red macule or papule and can expand up to 50 cm in diameter, with central clearing and clearly or slightly defined borders. Other symptoms may include headache, fever, fatigue, muscle and joint pain, which can lead to misdiagnosis or delayed treatment. If left untreated, the disease can cause serious systemic complications, including neurological disorders (e.g., meningitis, neuropathies), cardiac problems (atrioventricular block), and arthritis, most often affecting the knees. The late stages of the disease can last for months or years, but with adequate antibiotic therapy, symptoms can often be reduced. Diagnosis is based on the clinical presentation and serological tests such as ELISA and Western blot, which detect the presence of antibodies to the bacteria. It is important to note that serological tests may be negative in the early phase of infection, as antibodies have not yet developed. PCR tests can confirm the presence of bacteria through direct examination of blood, cerebrospinal fluid, or tissue samples. However, in routine diagnosis, the presence of erythema migrans as a clinical finding is considered a sufficient reason to initiate therapy. Prevention focuses on reducing contact with ticks, including wearing appropriate protective clothing, using repellents, and treating clothing with permethrin. Preventive measures also include mowing and maintaining grassy areas, as well as controlling rodent and tick populations in places where people live or spend time.

**Keywords:** Lyme disease, Borrelia burgdorferi, Ixodes ricinus, vector-borne infection, erythema migrans, bacterial transmission, diagnosis, serological tests, prevention, complications, arthritis, neurological disorders, ticks, and rodents

## DEFINITION AND EPIDEMIOLOGY OF LYME DISEASE

Lyme disease (LD), or MORBUS LYME, is a chronic multisystem infectious disease in humans, transmitted through the bite of an infected hard tick, Ixodes ricinus, carrying one of the bacteria such as Borrelia burgdorferi (Bb) (Figure 1), and less commonly other Borrelia species: Borrelia garinii (Bg) and Borrelia afzelii (Ba).

It is a multisystem disease that can affect the skin, joints, heart, and nervous system. Lyme disease is particularly known for its frequent manifestation as the characteristic “erythema migrans”, a bull’s-eye-shaped skin rash [1].

**Figure 1.** *Borrelia burgdorferi* magnified 400 x

Source: https://upload.wikimedia.org/wikipedia/commons/f/f3/Borrelia_burgdorferi_%28CDC-PHIL_-6631%29_lores.jpg

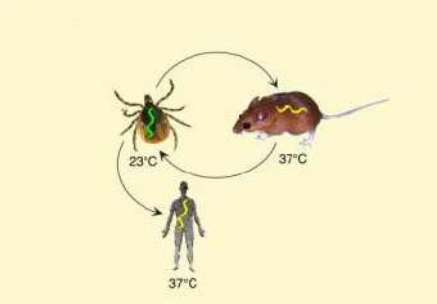
Kada se govori o razvojnim stadijumima krpelja treba poći od jaja, koje u rano proleće položi ženka (adult). Iz njih se u rano leto izlegu larve. Larva uzima krvni obrok na najbližoj životinji. Najčešće su to mikromamalije (šumski, poljski glodari, ježevi, ali i druge). Čovek takođe može biti žrtva uboda larve ali daleko ređe u odnosu na druge razvojne stadijume krpelja. Larva se presvlači (sazreva) u nimfu i uzima drugi krvni obrok i to od najbliže životinje. Kod nimfe to su zečevi, ptice, jeleni, pa i čovek ukoliko boravi u prirodnom staništu krpelja. Borelije se prenose salivom krpelja tokom uzimanja obroka u period od 48h iIi duže. Postoje tri teorije o načinu prenosa Bb iz krpelja u sledećeg domaćina. Dve su najzastupljenije. Jedna je da krpelj tokom halapljivog sisanja krvi, u jednom trenutku kad se nasisa krvi, povrati svoj crevni sadržaj (Bb se nalazi u srednjem crevu krpelja). Druga koja govori o migraciji Bb iz creva u glandularne žlezde, je manje zastupljena, ali prihvaćena u literaturi [1,2]. Ova teorija sugeriše da se radi o prenosu uzročnika kao što to rade npr. komarci kad prenose plasmodiuma. Ovu teoriju najčešće zastupaju oni koji svaki ubod krpelja tretiraju profilaktički antibioticima, što je pogrešno.

U radovima koji su se bavili eksperimentalno prenosom Borelije sa zaraženog krpelja na miša, pokazano je da se prvih 24h boravka krpelja u koži retko javljala zaraženost. Ona je rasla sa dužinom boravka – 48h, a pogotovo nakon 72h. Zato nam je podatak o boravku krpelja, manje od 24h jako važan u prevenciji nastanka Lb. Promptnim skidanjem krpelja, na adekvatan način, unutar prvih časova boravka u koži može biti odlučujuće, ukoliko je krpelj bio zaražen Bb [3]. Kod Lajmske bolesti rezervoar je ekološka niša, mesto u domaćinu (krpelj, mišoliki glodar i dr) gde uzročnik živi, održava se kao vrsta i/ili razmnožava se, najčešće ne oštećujući svog domaćina.

Kod Lajmske bolesti krpelj može biti i rezervoar Bb, ali i IZVOR zaraze (onaj koji je neposredno zarazi domaćina Bb). Jednom zaražen krpelj, od larve do adultnih oblika, prenosi Bb, pa čak i transovarijalno. Vektor, ili prenosilac uzročnika je Ixodes ricinus (Evropa), Ixodes pacificus i Ixodes scapularis (Amerika), Ixodes persulcatus (Azija) itd. a izazivač bolesti genospecies Bb [4,5].

Termin „ciklus borelije“ se prevodi kao životni ciklus borelije ili enzootski ciklus borelije na engleskom, što se odnosi na složeni životni ciklus bakterije lajmske bolesti (Borrelia burgdorferi) koja se smenjuje između vektora krpelja i kičmenjaka domaćina. Ovaj „enzootski“ ciklus uključuje prenos bakterije sa zaraženog krpelja na domaćina, a zatim potencijalno nazad na drugog krpelja (Slika .2) [6].

**Slika 2.** Životni ciklus (ciklus prenošenja) borelije koja se smenjuje između vektora krpelja i kičmenjaka domaćina.
preuzeto sa: https://upload.wikimedia.org/wikipedia/commons/0/08/Borrelia_cycle.jpg




## KLINIČKI ASPEKTI LAJMSKE BOLESTI

Lajmska bolest je najčešće vektorsko infektivno oboljenje na prostoru Evrope i Amerike. Lb je tipično sezonsko oboljenje. Javlja se u periodu aktivnosti krpelja: od ranog proleća i prvih toplih dana (nimfa), tokom juna (larva i nimfa), pa sve do kasnih jesenjih dana (adult). Tokom ostalog perioda godine, kad prestaje aktivnost krpelja, ne nastaje Lb. Tragajući za dijagnozom kod pacijenta sa izraženim simptomima koji podsećaju na Lb, najčešće se, preko serološki nalaza, može posumnjati na Lb. Inkubacioni period je 3-30 dana, od uboda krpelja do pojave simptoma i znakova Lb. Nije svaki eritem na mestu uboda krpelja – Erythema

When discussing the developmental stages of ticks, the starting point is the egg, which the female (adult) lays in early spring. From these eggs, larvae hatch in early summer. The larva takes its first blood meal from the nearest available animal—most often micromammals (forest and field rodents, hedgehogs, and others). Humans can also occasionally be bitten by larvae, although this occurs much less frequently compared to other developmental stages of the tick.

After feeding, the larva molts (matures) into a nymph, which then takes a second blood meal from the nearest host. For nymphs, these hosts typically include hares, birds, deer, and occasionally humans who spend time in tick habitats. Borrelia is transmitted through tick saliva during feeding, usually after 48 hours or longer.

There are three theories regarding the transmission of Borrelia burgdorferi (Bb) from the tick to the next host, with two being most widely accepted. The first suggests that during the tick's intense blood-feeding phase, once it becomes engorged, it regurgitates part of its intestinal contents (Bb resides in the tick's midgut). The second, less common but still recognized in the literature [1,2], proposes that Bb migrates from the midgut to the salivary glands. This theory implies a transmission mechanism similar to that of mosquitoes transmitting Plasmodium. Advocates of this theory often recommend prophylactic antibiotic treatment after every tick bite, which is incorrect.

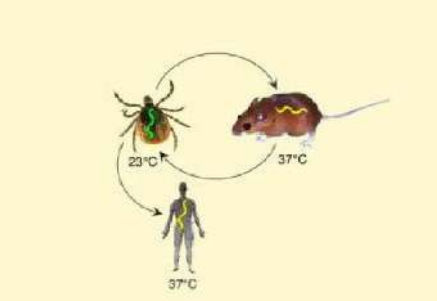
Experimental studies on the transmission of Borrelia from infected ticks to mice have shown that infection rarely occurs within the first 24 hours of tick attachment. The likelihood of infection increases with the tick's duration of attachment—particularly after 48 hours, and especially after 72 hours. Therefore, information about the tick's attachment time (less than 24 hours) is extremely important for the prevention of Lyme disease. Prompt and proper removal of the tick within the first few hours can be crucial, especially if the tick is infected with Bb [3].

In Lyme disease, the reservoir represents the ecological niche—the place within the host (tick, small rodent, etc.) where the pathogen lives, persists as a species, and/or reproduces, usually without harming its host.

In the case of Lyme disease, the tick can serve both as a reservoir of Bb and as the source of infection (the one that directly transmits Bb to a new host). Once infected, a tick can transmit Bb throughout all its developmental stages—from larva to adult—and even transovarially (from female to offspring). The vector, or carrier of the pathogen, is Ixodes ricinus (Europe), Ixodes pacificus and Ixodes scapularis (America), Ixodes persulcatus (Asia), etc., while the causative agent belongs to the Borrelia burgdorferi genospecies [4,5].

The term "Borrelia cycle" is translated as either the life cycle of Borrelia or the enzootic cycle of Borrelia in English. It refers to the complex life cycle of the Lyme disease bacterium (Borrelia burgdorferi), which alternates between tick vectors and vertebrate hosts. This enzootic cycle involves the transmission of the bacterium from an infected tick to a host, and potentially back to another tick (Figure 2) [6].

**Figure 2.** life cycle (transmission cycle) of Borrelia, which alternates between the tick vector and the vertebrate host.
Source: https://upload.wikimedia.org/wikipedia/commons/0/08/Borrelia_cycle.jpg




**CLINICAL ASPECTS OF LYME DISEASE**

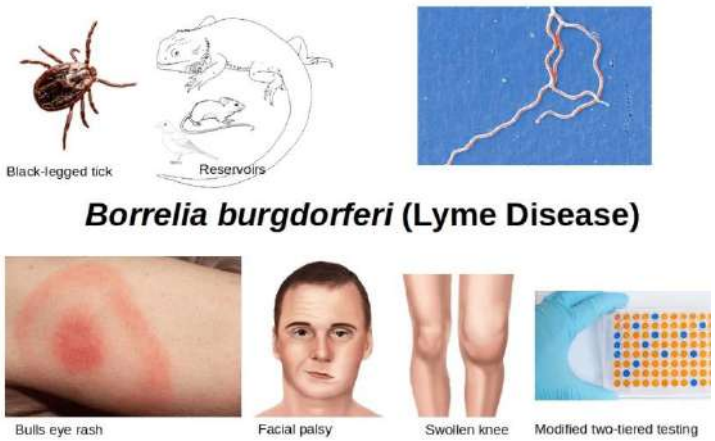
Lyme disease is the most common vector-borne infectious disease in Europe and North America. LD is typically a seasonal illness, occurring during periods of tick activity—from early spring and the first warm days (nymphal

migrans (EM). Erythema migrans se javlja u 60-80% slučajeva, a prate je simptomi slični gripu. Na mestu uboda krpelja, u period ne kraćem od 5-7 dana, može da se javi karakteristična kožna promena – Erythema migrans koja počinje kao makula ili papula i povećava čak do 50 cm. EM je crvenilo koje se javlja oko uboda krpelja koje se širi od centra ka periferiji u vidu nepravilnih koncentričnih krugova, nazubljenih ivica koje su jače crvene. Crvenilo je u ravni kože, toplo kao i ostali deo kože, ne daje osećaj bola ni svraba [7,8,9].

Ovako opisana kožna promena - EM je znak lajmske bolesti. Razlikuje se od drugih crvenila na koži jer nema tumor i dolor, a kalor je kao i kod ostalog dela kože [10]. Pored lezije (EM) kao rani simptomi (mogu se javiti simptomi slični gripu) se javljaju glavobolja, povišena temperature (vrlo retko), jeza, groznica (retko), bolovi u mišićima i kostima (zglobovima) i limfadenopatija. Umor (bezrazložan, nije vezan za fizičku aktivnost), vrlo jak i dugotrajan je vrlo čest simptom [10,11]. Simptomi traju oko 4 nedelje [11].

Kod nelečenih pacijenata dolazi nakon nekoliko nedelja do hematogene diseminacije i sistemskih znakova bolesti koji se karakterišu iznurenošću, mijalgijom, kožnim, srčanim, neurološkim poremećajima [10,11]. Kod 60% pacijenata razvija se artritis (monoartikularni ili oligoartikularni) koji uglavnom uključuje koleno. Ovde je već kasna faza Lb (treći stadijum) [10,12]. Kod 10-20% pacijenata se javljaju neurološke promene najčešće paraliza facijalnog nerva. Ova promena spada u sekundarni stadijum i nije tipična za naše krajeve. Centar za kontrolu i prevenciju bolesti (CDC) (eng. Centers for Disease Control and Prevention) ovaj simptom navodi kao čest u SAD [12]. Drugi stadijum - Karditis se javlja u oko 8% nelečenih, inficiranih osoba i manifestuje se palpitacijama koje su udružene sa abnormalnostima provodljivosti u AV čvoru i elektrokardiografskim promenama u S-T segmentu i T talasu [10,12]. Kasni stadijum, nakon više meseci i godina, kod nelečene Lajmske bolesti dovodi do artritisa više zglobova i pojave hroničnih lezija na koži sa diskolorizacijom- *acrodermatitis chronica atrophicans* [11,13].

**Slika 3.** Borrelia Burgdorferi - Lajmska bolest
preuzeto sa: https://i0.wp.com/microbeonline.com/wp-content/uploads/2021/05/Borrelia-Burgdorferi-Lyme-Disease-min.png?ssl=1




Produženo zadržavanje krpelja u koži povećava verovatnoću prenosa *Borrelia burgdorferi*. Stoga je pravovremeno uklanjanje krpelja od izuzetnog značaja za smanjenje rizika od infekcije. Što je duže vreme pričvršćenosti krpelja, to je veća mogućnost transmisije patogena. Iz tog razloga, brzo i adekvatno uklanjanje krpelja predstavlja jedan od najvažnijih koraka u prevenciji kliničke manifestacije lajmske bolesti [14,15].

Ukoliko se krpelj uoči na telu, preporučuje se njegovo što hitnije uklanjanje [16,17]. Idealno je da se to obavi u zdravstvenoj ustanovi, gde lekar može proceniti rizik od infekcije i odlučiti o daljem postupanju. Ako to trenutno nije moguće, krpelj se može ukloniti

stage), throughout June (larval and nymphal stages), and up to the late autumn months (adult stage). During the rest of the year, when tick activity ceases, Lyme disease does not occur.

When searching for a diagnosis in patients presenting with symptoms suggestive of LD, serological testing is most commonly used to raise clinical suspicion. The incubation period ranges from 3 to 30 days, from the tick bite to the appearance of signs and symptoms of Lyme disease. It is important to note that not every erythema at the site of a tick bite is Erythema migrans (EM). EM occurs in 60–80% of cases and is often accompanied by flu-like symptoms.

At the site of the tick bite, within 5–7 days or longer, a characteristic skin lesion may appear—Erythema migrans—which begins as a macule or papule and can enlarge to as much as 50 cm in diameter. EM presents as redness expanding from the bite site toward the periphery in the form of irregular concentric rings with serrated, more intensely red edges. The redness is flat, warm to the touch (like surrounding skin), and does not cause pain or itching [7,8,9].

This characteristic skin lesion—EM—is a hallmark sign of Lyme disease. It differs from other skin rashes because it lacks tumor (swelling) and dolor (pain), and the calor (warmth) is the same as in surrounding skin [10]. Alongside the lesion (EM), early symptoms—often flu-like—may include headache, mild fever (rare), chills, shivering (rare), muscle and joint pain, lymphadenopathy, and fatigue, which is profound, persistent, and unrelated to physical activity [10,11]. Symptoms typically last around four weeks [11].

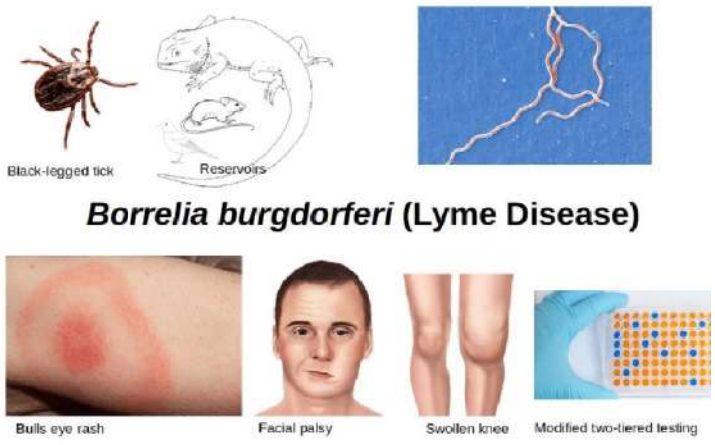
In untreated patients, after several weeks, hematogenous dissemination can occur, leading to systemic manifestations such as fatigue, myalgia, and skin, cardiac, and neurological disorders [10,11]. Arthritis develops in about 60% of patients, usually monoarticular or oligoarticular, predominantly affecting the knee joint—a sign of late-stage LD (third stage) [10,12].

Neurological manifestations occur in about 10–20% of patients, most commonly facial nerve palsy. This belongs to the secondary stage and is less common in Europe. The Centers for Disease Control and Prevention (CDC) identifies this symptom as frequent in the United States [12].

The second stage may also include carditis, occurring in approximately 8% of untreated, infected individuals, presenting with palpitations and atrioventricular (AV) conduction abnormalities, as well as electrocardiographic changes in the S-T segment and T wave [10,12].

The late stage, developing months or even years after untreated Lyme disease, leads to polyarthritis and chronic skin lesions with discoloration, known as acrodermatitis chronica atrophicans [11,13].

**Figure 3.** Borrelia Burgdorferi - Lyme disease
Source: https://i0.wp.com/microbeonline.com/wp-content/uploads/2021/05/Borrelia-Burgdorferi-Lyme-Disease-min.png?ssl=1



samostalno pomoću pincete sa tankim vrhovima. Pincetom treba obuhvatiti krpelja što bliže koži, u predelu neposredno iznad glave, i uz stalno, blago i ravnomerno povlačenje izvući ga iz kože bez naglih pokreta (Slika 4). Nakon uklanjanja, mesto uboda obavezno treba dezinfikovati alkoholom ili jodnim preparatom [18]. Bez obzira na uspešno uklanjanje, preporučuje se što raniji pregled kod lekara radi procene rizika, praćenja eventualnih simptoma i odluke o potrebi dalje dijagnostike ili profilaktičke terapije [17,19]. Najvažnije nije samo pravilno ukloniti krpelja, već i obavezno pratiti zdravstveno stanje i obratiti se lekaru, jer infekcija može nastupiti i kada je krpelj već uklonjen [16,17].

**Slika 4.** Uklanjanje krpelja pincetom
preuzeto sa: https://www.bbc.com/serbian/lat/svet-69247310

Ne preporučuje se rutinsko testiranje samih krpelja na prisustvo Borrelia burgdorferi ili drugih patogena u kliničke svrhe, jer pozitivan nalaz ne znači da je infekcija preneta, niti određuje terapijski pristup. Glavni kriterijumi za odluku o profilaktičkom lečenju su: vrsta krpelja (Ixodes), regija endemije, dužina pričvršćenosti (>36h), i vreme od uklanjanja (<72h). *(preporuka iz **IDSA/AAN/ACR smernica (2020)** za Lajmsku bolest)* [20].

## LABORATORIJSKA DIJAGNOSTIKA LAJMSKE BOLESTI

Laboratorijska dijagnostika Lajmske bolesti obuhvata kombinaciju metoda koje se primenjuju zavisno od faze bolesti i kliničke prezentacije [21,22]. Najpristupačnija i najčešće korišćena metoda je **serološko testiranje krvi** (ELISA, potvrda Western blot-om) [21,23], dok se kod sumnje na neuroboreliozu primenjuje serologija i PCR analiza **likvora** [22,24]**. PCR metoda** omogućava direktnu detekciju DNK *Borrelia burgdorferi* u krvi, likvoru ili specifičnim tkivima, ali negativan rezultat ne isključuje infekciju. Uklonjeni krpelji se mogu testirati PCR metodom za prisustvo patogena, ali takvo testiranje ima **isključivo epidemiološki značaj** i ne određuje terapijski pristup [21,25]. Pravilno tumačenje laboratorijskih nalaza zahteva integraciju rezultata sa kliničkom slikom i epidemiološkim faktorima, jer serološki testovi mogu dati lažno pozitivne ili negativne rezultate, naročito u ranim fazama bolesti.

Prolonged attachment of a tick to the skin increases the likelihood of transmitting Borrelia burgdorferi. Therefore, timely removal of the tick is crucial for reducing the risk of infection. The longer the tick remains attached, the higher the probability of pathogen transmission. For this reason, prompt and proper tick removal is one of the most important steps in preventing the clinical manifestation of Lyme disease [14,15].

If a tick is observed on the body, it is recommended to remove it as soon as possible [16,17]. Ideally, this should be done in a healthcare facility, where a physician can assess the risk of infection and determine further management. If immediate professional removal is not possible, the tick can be removed independently using fine-tipped tweezers. The tweezers should grasp the tick as close to the skin as possible, near its head, and pull it out slowly, steadily, and evenly without sudden movements (Figure 4).

After removal, the bite site should be disinfected with alcohol or iodine [18]. Regardless of successful removal, it is recommended to see a physician promptly to evaluate the risk, monitor for potential symptoms, and decide whether further diagnostic or prophylactic measures are needed [17,19]. The key is not only proper tick removal but also monitoring one's health and seeking medical attention, as infection can occur even after the tick has been removed [16,17].

**Figure 4.** Removing ticks with tweezers
Source: https://www.bbc.com/serbian/lat/svet-69247310

Routine testing of ticks themselves for the presence of Borrelia burgdorferi or other pathogens is not recommended for clinical purposes, as a positive result does not confirm that infection has been transmitted, nor does it determine therapeutic management. The main criteria for deciding on prophylactic treatment include: the tick species (Ixodes), endemic region, duration of attachment (>36 hours), and time since removal (<72 hours)—as recommended by the IDSA/AAN/ACR Lyme disease guidelines (2020) [20].

## LABORATORY DIAGNOSIS OF LYME DISEASE

The laboratory diagnosis of Lyme disease involves a combination of methods applied according to the stage of the disease and its clinical presentation [21,22]. The most accessible and widely used diagnostic approach is serological testing of blood samples (ELISA, confirmed by Western blot) [21,23]. In cases where neuroborreliosis is suspected, both serological testing and PCR analysis of cerebrospinal fluid (CSF) are performed [22,24].

The PCR method enables the direct detection of Borrelia burgdorferi DNA in blood, CSF, or specific tissue samples; however, a negative result does not exclude infection. Although removed ticks can also be tested by PCR for pathogen detection, such testing has epidemiological significance only and does not guide therapeutic decisions [21,25].

Proper interpretation of laboratory findings requires integration of test results with the clinical picture and epidemiological factors, since serological tests may yield false-positive or false-negative results, particularly in the early stages of the disease.

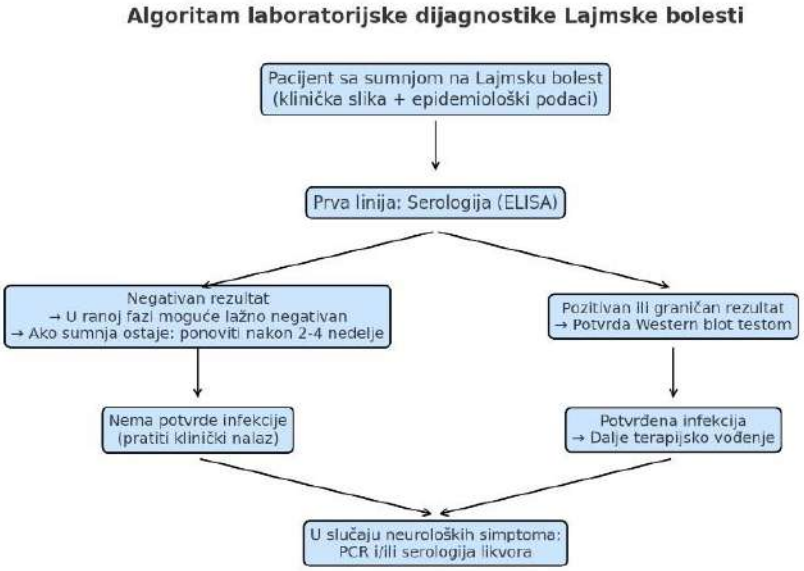



**Tabela 1.** Laboratorijska dijagnostika

| Uzorak | Metod | Prednosti | Ograničenja / Napomene |
|---|---|---|---|
| Krv | Serologija (ELISA → Western blot) | Najpristupačnija metoda, široko dostupna | Antitela se javljaju sporo (3–6 nedelja); lažno pozitivni i negativni rezultati mogu biti >20%; zahteva kliničku korelaciju |
| Krv | PCR | Mogućnost detekcije DNK u ranoj fazi bolesti | Negativan rezultat ne isključuje infekciju; osetljivost varira u različitim fazama bolesti |
| Likvor | Serologija / PCR | Korisno kod sumnje na neuroboreliozu | Invazivna procedura; rezultati zavise od faze bolesti |
| Sinovijalna tečnost / tkivo | PCR | Specifično kod artritisa ili lokalnih infekcija | Koristi se samo u selektovanim slučajevima; laboratorijski zahtevan proces |
| Krpelj | PCR | Utvrđivanje prisustva *Borrelia burgdorferi* (epidemiološki značaj) | Ne koristi se za kliničku dijagnostiku; nalaz ne određuje terapiju |

Krpelji se u kliničkoj praksi ne koriste za serološku dijagnostiku. Njihovo testiranje služi isključivo za epidemiološke svrhe ili istraživanja distribucije patogena. Serološki testovi u krvi i likvoru ostaju osnova rutinske laboratorijske dijagnostike Lajmske bolesti.

Serološki testovi su najpristupačniji (rade ih gotovo svi ZJZ) i rade se kao prvi korak u serološkoj dijagnostici Lajmske bolesti. Serološki testovi nisu ni posebno specifični, ni posebno senzitivni – daju i više od 20% "lažno pozitivnih" i "lažno negativnih" rezultata. Osim toga potrebno je naglasiti da se antitela na Bb sporo javljaju i da krv ne treba uzimati pre kraja treće, četvrte nedelje od početka tegoba. Treba biti oprezan kod tumačenja seroloških rezultata kod Lb.

Serološki testovi za dijagnostiku su ELISA test, imunofluorescentni testovi. ELISA testom (Slika 5) na *Borrelia burgdorferi* se vrši identifikacija prisustva At IgM I IgG klase, koja ukazuju na to da li reč o akutnoj infekciji (IgM) ili se radi o staroj infekciji (IgG) - (Prisustvo At IgG klase nije uvek kod Lb dokaz "stare" infekcije, kao kod drugih bolesti) [26,15].

IgM antitela se obično javljaju 2–4 nedelje od pojave lezije erythema migrans, ali nisu uvek prisutna u dovoljnoj meri da bi bila identifikovana serološkim testom i obično nestaju nakon 4–6 meseci. U nekim slučajevima, IgM klase se mogu identifikovati i mesecima nakon prve identifikacije. IgG antitela se javljaju obično 8–12 nedelja od početka bolesti i svoj pik dostižu za 4–6 meseci.

U serološkoj dijagnostici Lajmske bolesti, početni testovi uključuju ELISA, EIA (enzyme immunoassay) ili IFA (immunofluorescence antibody). Negativni

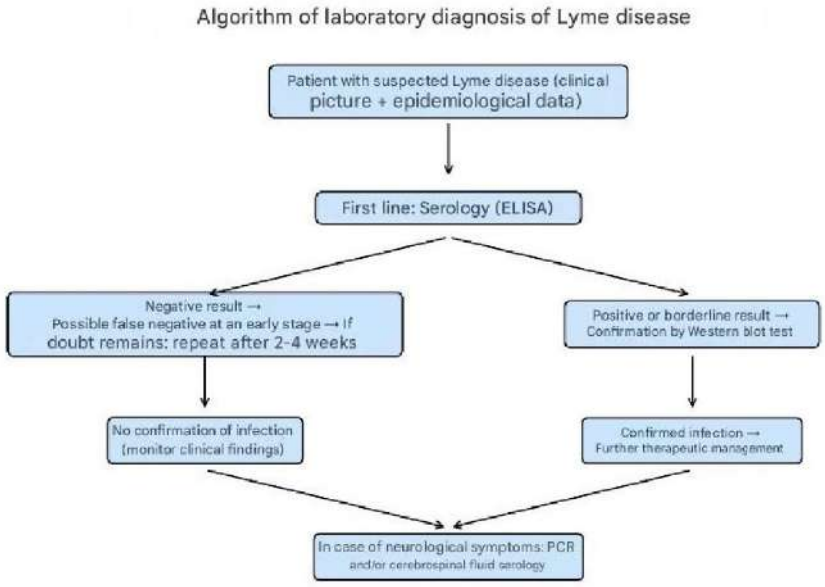



**Table 1**. Laboratory diagnostics

| Sample | Method | Advantages | Limitations / Notes |
|---|---|---|---|
| Blood | Serology (ELISA → Western blot) | The most affordable method, widely available | Antibodies appear slowly (3–6 weeks); false positive and negative results can be >20%; requires clinical correlation |
| Blood | PCR | The possibility of DNA detection in the early stages of the disease | A negative result does not rule out infection; sensitivity varies in different stages of the disease |
| CSF | Serology / PCR | Useful in suspected neuroborreliosis | Invasive procedure; results depend on the stage of the disease |
| Synovial fluid / tissue | PCR | Specifically for arthritis or local infections | It is used only in selected cases; laboratory required process |
| Tick | PCR | Determination of the presence of Borrelia burgdorferi (epidemiological significance) | It is not used for clinical diagnostics; the finding does not determine the therapy |

Ticks are not used for serological diagnosis in clinical practice. Their testing serves exclusively epidemiological purposes or research on the distribution of pathogens. Serological tests of blood and cerebrospinal fluid remain the cornerstone of routine laboratory diagnosis of Lyme disease.

Serological testing is the most accessible diagnostic approach (performed by almost all public health institutes) and represents the first step in the serological diagnosis of Lyme disease. However, these tests are neither highly specific nor highly sensitive, yielding more than 20% false-positive and false-negative results. It is also important to emphasize that antibodies to Borrelia burgdorferi develop slowly, and blood sampling should not be performed before the end of the third or fourth week after the onset of symptoms. Therefore, caution is required when interpreting serological results in Lyme disease.

The main serological tests used for diagnosis are ELISA and immunofluorescence assays (IFA). The ELISA test (Figure 5) for Borrelia burgdorferi identifies the presence of IgM and IgG antibodies, indicating whether it is an acute infection (IgM) or a past infection (IgG)—although it is important to note that the presence of IgG antibodies in Lyme disease does not always confirm a past infection, as it might in other diseases [26,15].

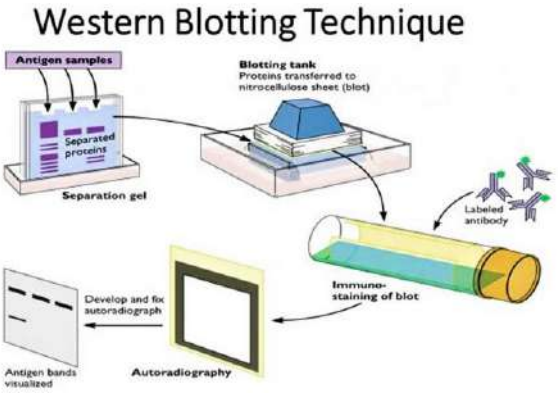
IgM antibodies usually appear 2–4 weeks after the onset of the erythema migrans lesion but are not always detectable at sufficient levels for serological identification and typically disappear after 4–6 months. In some cases, IgM antibodies may persist for several months after initial detection. IgG antibodies typically appear 8–12 weeks after the onset of illness and reach their peak within 4–6 months.

rezultati u ranoj fazi bolesti ne isključuju dijagnozu, jer antitela mogu još uvek biti nedovoljno razvijena, posebno kod ranog započinjanja antibiotske terapije ili dok je prisutna lezija erythema migrans. Pozitivni ili granični rezultati potvrđuju se Western imunoblot testom (Slika 6). Kod negativnih seroloških rezultata, a prisutnih kliničkih simptoma Lajmske bolesti, preporučuje se ponoviti testiranje nakon 2–4 nedelje [27,28].

**Slika 5.** Kako izabrati pravi elisa komplet

preuzeto sa: https://www.bmgrp.com/how-to-choose-the-right-elisa-kit/

**Slika 6.** Tehnika Western blotovanja, koja se koristi za detekciju specifičnih proteina u uzorcima
preuzeto sa: https://healthjade.net/western-blot/




Pored ovih testova u dijagnostici se ređe koristi PCR test, koji se preporučuje kod testiranja samog krpelja na prisustvo nekog od izazivača Lajmske bolesti (u istraživačke svrhe, a ne u rutinskoj dijagnostici). PCR je i jedina metoda u svakodnevnoj dijagnostici, osim kultivacije Borelija na BSK II podlozi, a koja se vrši samo u istraživanjima.

Lažno pozitivni serološki nalazi kod Lajmske bolesti mogu se javiti kod pacijenata sa sifilisom. Rana dijagnoza i pravovremena primena antimikrobne terapije imaju ključnu ulogu u prevenciji kardioloških, neuroloških i koštano-mišićnih komplikacija. Važno je napomenuti da antibiotici u inicijalnom stadijumu Lajmske bolesti ne predstavljaju prevenciju razvoja simptoma u kasnijim fazama, već služe kao profilaktički tretman koji smanjuje rizik od progresije bolesti.

## LEČENJE LAJMSKE BOLESTI

U terapiji rane Lajmske bolesti koriste se oralni antibiotici: amoksicilin, doksiciklin ili cefuroksim. Trajanje terapije i izbor leka zavise od starosne dobi pacijenta i kliničke faze bolesti. Kod dece mlađe od 8 godina doksiciklin se obično izbegava zbog potencijalnog efekta na zube i kosti, a kod trudnica se preferira amoksicilin.

Kod pacijenata sa rekurentnim artritisom ili zahvaćenim centralnim i perifernim nervnim sistemom, primenjuje se parenteralna terapija intravenoznim antibiotikom – najčešće ceftriaksonom, cefotaksimom ili penicilinom G. I.V. terapija se sprovodi kod težih i hroničnih oblika bolesti, pri čemu su ključni odgovarajuća doza, trajanje terapije i starost pacijenta, jer utiču na efikasnost lečenja i prevenciju komplikacija.

Terapija Lajmske bolesti zavisi od kliničkog oblika, težine bolesti i starosti pacijenta. U ranim lokalizovanim oblicima primenjuju se oralni antibiotici – doksiciklin, amoksicilin ili cefuroksim – pri čemu je izbor leka ograničen kod dece mlađe od 8 godina i trudnica. Trajanje terapije varira od 10 do 21 dana, zavisno od leka i kliničke slike. Kod težih i hroničnih oblika, uključujući neuroboreliozu i rekurentni artritis, primenjuje se parenteralna terapija intravenoznim ceftriaksonom, cefotaksimom ili penicilinom G, obično 14–28 dana. Efikasnost lečenja zavisi od pravovremene primene, odgovarajuće doze i dužine terapije, kao i od uzrasta pacijenta [29,30].

In the serological diagnosis of Lyme disease, the initial tests include ELISA, EIA (enzyme immunoassay), or IFA (immunofluorescence antibody assay). Negative results in the early phase of the disease do not exclude the diagnosis, as antibodies may still be insufficiently developed—particularly if antibiotic therapy was initiated early or if erythema migrans is still present. Positive or borderline results should be confirmed using the Western immunoblot test (Figure 6).

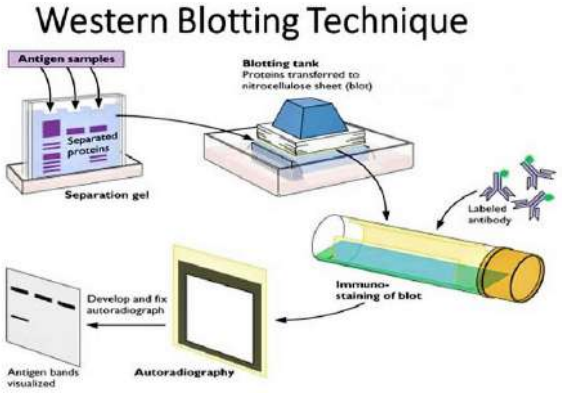
If serological results are negative, but clinical symptoms of Lyme disease persist, it is recommended to repeat testing after 2–4 weeks [27,28].

**Figure 5.** How to choose the right propeller kit

Source: https://www.bmgrp.com/how-to-choose-the-right-elisa-kit/

**Figure 6.** Western blotting technique, used to detect specific proteins in samples

Source: https://healthjade.net/western-blot/




In addition to these tests, PCR is less commonly used in diagnostics and is recommended for testing the tick itself for the presence of Lyme disease pathogens (primarily for research purposes, not routine diagnostics). PCR is also the only method used in everyday diagnostics, apart from the cultivation of Borrelia on BSK II medium, which is performed only in research settings.

False-positive serological results for Lyme disease can occur in patients with syphilis. Early diagnosis and timely administration of antimicrobial therapy play a key role in preventing cardiac, neurological, and musculoskeletal complications. It is important to note that antibiotics in the initial stage of Lyme disease do not prevent the development of symptoms in later stages but serve as prophylactic treatment to reduce the risk of disease progression..

## TREATMENT OF LYME DISEASE

In the treatment of early Lyme disease, oral antibiotics such as amoxicillin, doxycycline, or cefuroxime are used. The choice of antibiotic and duration of therapy depend on the patient's age and the clinical stage of the disease. Doxycycline is generally avoided in children under 8 years due to potential effects on teeth and bones, while amoxicillin is preferred in pregnant women.

For patients with recurrent arthritis or involvement of the central or peripheral nervous system, parenteral therapy with intravenous antibiotics—most commonly ceftriaxone, cefotaxime, or penicillin G—is administered. IV therapy is reserved for severe or chronic forms of the disease, with dose, duration, and patient age being crucial factors for treatment effectiveness and complication prevention.

Lyme disease therapy is guided by the clinical form, disease severity, and patient age. In early localized forms, oral antibiotics—doxycycline, amoxicillin, or cefuroxime—are prescribed, with restrictions for children under 8 years and pregnant women. Treatment duration ranges from 10 to 21 days, depending on the antibiotic and clinical presentation. For more severe or chronic forms, including neuroborreliosis and recurrent arthritis, parenteral therapy with intravenous ceftriaxone, cefotaxime, or penicillin G is used, typically for 14–28 days. Treatment efficacy depends on timely administration, appropriate dosage, therapy duration, and patient age. [29,30].

**Tabela 2.** Terapija Lajmske bolesti: Antibiotici, doze i trajanje

| Oblik Lajmske bolesti | Antibiotik | Doza (odrasli) | Trajanje terapije | Napomene / uzrast |
|---|---|---|---|---|
| Rani lokalizovani (erythema migrans) | Doksiciklin | 100 mg oralno 2× dnevno | 10–21 dana | Ne preporučuje se kod dece <8 godina; ne za trudnice |
| | Amoksicilin | 500 mg oralno 3× dnevno | 14–21 dana | Pogodan za decu i trudnice |
| | Cefuroksim axetil | 500 mg oralno 2× dnevno | 14–21 dana | Alternativa za decu i odrasle |
| Rani diseminovani / neuroborelioza | Ceftriakson i.v. | 2 g dnevno | 14–28 dana | Primena kod težih i hroničnih oblika |
| | Cefotaksim i.v. | 2 g svakih 8 h | 14–28 dana | - |
| | Penicilin G i.v. | 18–24 miliona IU dnevno u 4–6 doza | 14–28 dana | - |
| Rekurentni artritis / centralni i periferni nervni sistem | Ceftriakson i.v. | 2 g dnevno | 14–28 dana | Teži oblici bolesti, starost pacijenta utiče na dozu |
| | Cefotaksim i.v. | 2 g svakih 8 h | 14–28 dana | - |
| | Penicilin G i.v. | 18–24 miliona IU dnevno u 4–6 doza | 14–28 dana | - |

**Napomene:** Doksiciklin se ne koristi kod dece mlađe od 8 godina i trudnica zbog rizika za zube i kosti. Oralna terapija se primenjuje u ranim lokalizovanim oblicima. I.V. terapija se koristi kod težih, diseminovanih ili hroničnih oblika, kod neuroborelioze i rekurentnog artritisa. Dužina terapije može se prilagoditi kliničkom odgovoru pacijenta.

## PREVENCIJA

Suzbijanje krpelja na područjima gde ljudi često borave (parkovi, park-šume, rekreativne površine) predstavlja osnovnu meru u prevenciji uboda i samim tim smanjenju rizika od prenosa lajmske bolesti. Preventivne aktivnosti se mogu podeliti na **ekološke mere kontrole**, **lične mere zaštite** i **javnozdravstvene intervencije**:

***Ekološke mere kontrole*** su primena odgovarajućih antiparazitarnih sredstava (akaricida) na ograničenim površinama gde je registrovana visoka populacija krpelja, košenje i održavanje travnatih površina, posebno na mestima koja se koriste za rekreaciju i igru, uklanjanje lišća, niskog rastinja i granja u parkovima i dvorištima, čime se smanjuju staništa pogodna za krpelje, kontrola populacije glodara, koji su prirodni rezervoari *Borrelia burgdorferi*, kao i smanjenje kontakta između glodara i ljudi.

***U lične mere zaštite*** spada nošenje adekvatne odeće prilikom boravka u prirodi: dugih rukava, dugih pantalona uvučenih u čarape, zatvorene obuće i svetle odeće koja olakšava uočavanje krpelja, korišćenje repelenata na bazi DEET-a, ikaridina ili permatrina (na odeći), posebno kod osoba koje provode duže vreme na otvorenom u endemskim područjima kao i pregled celog tela nakon boravka u prirodi, uključujući kosu, pregibe i delove kože gde se krpelji najčešće zakače.

***Javnozdravstvene intervencije*** su edukacija stanovništva o rizicima uboda krpelja, načinima zaštite i značaju ranog uklanjanja krpelja, organizovane akcije suzbijanja krpelja na javnim površinama tokom sezone njihove najveće aktivnosti (proleće i leto), praćenje i nadzor populacije krpelja u endemskim područjima, kao i mapiranje rizika za stanovništvo [31-33].

## ZAKLJUČAK

Lajmska bolest predstavlja značajan javnozdravstveni problem u endemskim područjima Evrope i Severne Amerike. Prevencija se zasniva na smanjenju kontakta sa krpeljima, nošenju zaštitne odeće, primeni repelenata i ekološkim merama kontrole populacije krpelja i glodara. Dijagnoza se uglavnom postavlja klinički, uz potvrdu serološkim testovima, dok molekularne metode služe kao dopunska dijagnostika. Pravovremena i adekvatna terapija antibiotikom u ranoj fazi bolesti ključna je za sprečavanje sistemskih komplikacija. Edukacija stanovništva i medicinskog osoblja, kao i pravilno uklanjanje krpelja, predstavljaju najefikasnije strategije u kontroli i prevenciji lajmske bolesti.

**Table 2.** Lyme Disease Therapy: Antibiotics, Dosages, and Duration

| Form of Lyme disease | Antibiotic | Dose (adult) | Duration of therapy | Notes / age |
|---|---|---|---|---|
| Early localized (erythema migrans) | Doxycycline | 100 mg orally 2× daily | 10–21 days | Not recommended for children <8 years; not for pregnant women |
| | Amoxicillin | 500 mg orally 3× daily | 14–21 days | Suitable for children and pregnant women |
| | Cefuroxime axetil | 500 mg orally 2× daily | 14–21 days | Alternative for children and adults |
| Early disseminated / neuroborreliosis | Ceftriaxone i.v. | 2 g daily | 14–28 days | Application in severe and chronic forms |
| | Cefotaxime i.v. | 2 g every 8 hours | 14–28 days | - |
| | Penicillin G i.v. | 18–24 million IU per day in 4–6 doses | 14–28 days | - |
| Recurrent arthritis / central and peripheral nervous system | Ceftriaxone i.v. | 2 g daily | 14–28 days | More severe forms of the disease, the age of the patient affects the dose |
| | Cefotaxime i.v. | 2 g every 8 h | 14–28 days | - |
| | Penicillin G i.v. | 18–24 miliona IU per day in 4–6 doses | 14–28 days | - |

**Notes:** Doxycycline is not used in children under 8 years of age and in pregnant women due to the risk to teeth and bones. Oral therapy is applied in early localized forms. I.V. therapy is used in severe, disseminated, or chronic forms, in cases of neuroborreliosis and recurrent arthritis. The duration of therapy can be adjusted according to the patient's clinical response..

## PREVENTION

Control of ticks in areas frequently visited by people (parks, forested parks, recreational areas) represents a fundamental measure for preventing tick bites and, consequently, reducing the risk of Lyme disease transmission. Preventive activities can be divided into ecological control measures, personal protective measures, and public health interventions:

***Ecological control measures*** include the application of appropriate acaricides on limited areas with high tick populations, mowing and maintenance of grassy areas—especially in places used for recreation and play—removal of leaves, low vegetation, and branches in parks and yards to reduce suitable tick habitats, control of rodent populations that are natural reservoirs of Borrelia burgdorferi, and minimizing human-rodent contact.

***Personal protective measures*** involve wearing appropriate clothing when in nature: long sleeves, long pants tucked into socks, closed shoes, and light-colored clothing to facilitate tick detection; using repellents based on DEET, icaridin, or permethrin (on clothing), especially for individuals spending extended time outdoors in endemic areas; and performing a full-body tick check after outdoor activities, including hair, skin folds, and areas where ticks commonly attach.

***Public health interventions*** include educating the population about the risks of tick bites, protection methods, and the importance of early tick removal; organizing tick control campaigns in public areas during peak activity seasons (spring and summer); monitoring and surveillance of tick populations in endemic regions; and risk mapping for the local population. [31-33].

## CONCLUSION

Lyme disease represents a significant public health problem in endemic areas of Europe and North America. Prevention is based on reducing contact with ticks, wearing protective clothing, using repellents, and implementing ecological measures to control tick and rodent populations. Diagnosis is primarily clinical, supported by serological testing, while molecular methods serve as supplementary diagnostic tools. Timely and appropriate antibiotic therapy in the early stage of the disease is crucial for preventing systemic complications. Educating the public and healthcare personnel, as well as proper tick removal, are the most effective strategies for controlling and preventing Lyme disease.

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Pregledni članak

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# ДИЈАГНОЗА И ТРЕТМАН ПЕЛВИЧНЕ ВЕНСКЕ КОНГЕСТИЈЕ КОД ЖЕНА

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1) ДОМ ЗДРАВЉА СРЕМСКА МИТРОВИЦА, СЛУЖБА ЗА ЗДРАВСТВЕНУ ЗАШТИТУ ЖЕНА, СРЕМСКА МИТРОВИЦА; 2) КЛИНИЧКО БОЛНИЧКИ ЦЕНТАР КОСОВСКА МИТРОВИЦА, ОДЕЉЕЊЕ ГИНЕКОЛОГИЈЕ И АКУШЕРСТВА, СРБИЈА; 3) КЛИНИЧКО БОЛНИЧКИ ЦЕНТАР „ДР ДРАГИША МИШОВИЋ-ДЕДИЊЕ“, БОЛНИЦА ЗА ГИНЕКОЛОГИЈУ И АКУШЕРСТВО, БЕОГРАД; 4) ГИНЕКОЛОШКО АКУШЕРСКА ОРДИНАЦИЈА РАДОЈЧИЋ, БЕОГРАД; 5) ДОМ ЗДРАВЉА СРЕМСКА МИТРОВИЦА, СЛУЖБА ОПШТЕ МЕДИЦИНЕ, СРЕМСКА МИТРОВИЦА

**Сажетак: Увод:** Пелвични венски конгестивни синдром (ПВКС) се може дефинисати као поремећај у венском систему карлице, односно постојање пелвичне венске инсуфицијенције (ПВИ) која се манифестује широким спектром симптома и знакова. ПВКС погађа жене у репродуктивном добу и често се јавља са хроничним болом у карлици. Остали симптоми укључују осећај тежине у карлици, диспареунију, дисменореју, лумбалну бол, учестало и ургентно мокрење и знаке проширених вулварних, перинеалних, глутеалних површних вена или венских варикса доњих екстремитета и хемороида. ПВИ може бити узрокована комбинацијом више фактора: генетском предиспозицијом, анатомским абнормалностима, хормонским факторима, дисфункционалним залисцима, опструкцијом венског тока и оштећењем зидова вена. **Дијагностика:** Дијагноза ПВКС и даље представља велики изазов, с обзиром на недостатак универзално прихваћених критеријума у дијагностичким имиџинг модалитетима. За дијагностиковање се могу користити следеће имиџинг методе: ултразвук (УЗ), компјутеризована томографија (ЦТ), магнетна резонанца (МР) као неинвазивне методе и венографија (ВГ) као инвазивна метода. Ултразвук карлице је обично метода прве линије. Транскатетерска венографија и даље остаје златни стандард за дијагнозу ПВКС. **Третман:** Конзервативни третман медикаментима за ПВКС је ограничен јер недостају подаци о дугорочној ефикасности. Компресија је једна од терапијских опција конзервативног третмана. Емболизација се препоручује за лечење ПВКС. Клиничко побољшање након емболизације креће се у различитим студијама од 47 до 100% али су потребна будућа рандомизована испитивања у циљу одређивања јасних протокола у управљању емболизацијом. **Закључак**: ПВКС је чест је узрочник хроничног пелвичног бола код жена али се због недовољног познавања, често не препознаје и остаје недијагностикован. У недостатку осталих узрока ПВКС, треба помислити и на ПВИ. Потребна је додатна едукација гинеколога за примену УЗ у циљу дијагностике ПВКС с обзиром да је УЗ иницијална имиџинг метода.

**Кључне речи:** пелвични конгестивни синдром, пелвична венска инсуфицијенција, хронична пелвична бол, емболизација.

## УВОД

Пелвични венски конгестивни синдром (ПВКС) се може дефинисати као поремећај у венском систему карлице, односно постојање пелвичне венске инсуфицијенције (ПВИ) која се манифестује широким спектром симптома и знакова. Из дефиниције произилази да је основни узрок овог синдрома пелвична венска инсуфицијенција, на коју указује дилатација и дисфукција оваријалних вена и унутрашњих илијачних вена са њеним притокама као и венским плексусима.

ПВКС погађа жене у репродуктивном добу и често се јавља са хроничним болом у карлици, најмање шест месеци [1]. Често се бол описивао као типичан симптом повезан са ПВКС, који је окарактерисан као хроничан, туп, једностран или билатералан [2]. Остали симптоми укључују осећај тежине у карлици, диспареунију, дисменорејy, лумбалну бол, учестало и ургентно мокрење и знаке проширених вулварних, перинеалних,



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TIMOK MEDICAL GAZETTE

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# DIAGNOSIS AND TREATMENT OF PELVIC VENOUS CONGESTION IN WOMEN

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**Abstract: Introduction:** Pelvic venous congestion syndrome (PVCS) can be defined as a disorder of the pelvic venous system, i.e. the presence of pelvic venous insufficiency (PVI) that manifests itself with a wide range of symptoms and signs. PVCS affects women of reproductive age and often presents with chronic pelvic pain. Other symptoms include pelvic heaviness, dyspareunia, dysmenorrhea, low back pain, frequent and urgent urination, and signs of dilated vulvar, perineal, gluteal superficial veins or varicose veins of the lower extremities and hemorrhoids. PVCS can be caused by a combination of several factors: genetic predisposition, anatomical abnormalities, hormonal factors, dysfunctional valves, obstruction of venous flow, and damage to the vein walls. Diagnostics: The diagnosis of PVCS remains a major challenge, given the lack of universally accepted criteria in diagnostic imaging modalities. The following imaging methods can be used for diagnosis: ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) as non-invasive methods and venography (VG) as an invasive method. Pelvic ultrasound is usually the first-line method. Transcatheter venography remains the gold standard for the diagnosis of PVCS. Treatment: Conservative medical treatment for PVCS is limited due to the lack of data on long-term efficacy. Compression is one of the therapeutic options for conservative treatment. Embolization is recommended for the treatment of PVCS. Clinical improvement after embolization ranges from 47 to 100% in different studies, but future randomized trials are needed to determine clear protocols for the management of embolization. Conclusion: PVCS is a common cause of chronic pelvic pain in women, but due to lack of knowledge, it is often not recognized and remains undiagnosed. In the absence of other causes of PVCS, PVI should also be considered. Additional education of gynecologists for the use of ultrasound in the diagnosis of PVCS is needed, given that ultrasound is the initial imaging method.

**Key words:** pelvic congestive syndrome, pelvic venous insufficiency, chronic pelvic pain, embolization.

## INTRODUCTION

Pelvic venous congestive syndrome (PVCS) can be defined as a disorder of the pelvic venous system, namely the presence of pelvic venous insufficiency (PVI), which manifests through a wide spectrum of symptoms and signs. By definition, the primary cause of this syndrome is pelvic venous insufficiency, indicated by dilation and dysfunction of the ovarian veins, internal iliac veins with their tributaries, as well as venous plexuses.

PVCS affects women of reproductive age and is often associated with chronic pelvic pain lasting at least six months [1]. Pain is frequently described as a typical symptom of PVCS, characterized as chronic, dull, unilateral or bilateral [2]. Other symptoms include a feeling of pelvic heaviness, dyspareunia,

глутеалних површних вена или венских варикса доњих екстремитета и хемороида [1]. Хронична бол у карлици није неопходна за дијагнозу, јер су код многих пацијената преовлађујући симптоми атипичне површинске варикозе. Код одређеног броја жена површинске варикозне вене могу бити и једини знак ПВИ. Преваленција варикозитета вулве код пацијената са ПВКС је чак 24–40%. До 80% пацијената са венском дилатацијом карлице могу се уочити различити степени удружене венске инсуфицијенције доњих екстремитета [2]. Сложеност проблема је у чињеници да се различите тегобе могу јавити код истог степена ПВИ баш као што се исте тегобе јављају код различитих степена ПВИ. Хронична пелвична бол се код жена може јавити из различитих разлога, укључујући ендометриозу, адхезије, миоме, аденомиозу, пролапс гениталних органа, малигне процесе и многе друге узроке а врло често се у недостатку објашњења узрока бола, хронична бол приписује психосоматским поремећајима. Због неспецифичне симптоматологије ПВКС је врло често непрепознат и недовољно дијагностикован. Фактори који појачавају бол у карлици описани у литератури су дуги периоди стајања, ходања или седења као и фактори који повећавају абдоминални притисак као што су подизање и трудноћа. Бол се генерално погоршава током дана, а такође и пре и у првим данима менструације а смањује се приликом лежања.

Бол се такође повећава током и након сексуалног односа. Осман и др. су објавили да је диспареунија због ендометриозе типично повезана са дубоком пенетрацијом, док се бол због ПВКС обично погоршава сексуалним односом, изазивајући пулсирајући бол након односа [3]. У ПВКС се могу се јавити уринарни симптоми због перивезикалних варикозитета као што су раздражљивост бешике и императивни нагон за мокрењем(ургентност) или дизурија. Остале манифестације ПВКС-а такође могу укључивати ректалну нелагодност, отечену вулву, вагинални исцедак, упорно генитално узбуђење и неспецифичне гастроинтестиналне симптоме као што су надимање и мучнина. Хронични карлични бол и додатни симптоми негативно утичу на квалитет живота пацијената, што се у овој групи доводи у значајно чешћу депресију, анксиозност и генерализовану летаргију [1].

***Анатомија***

Пелвични венски систем је одговоран за прикупљање венске крви из зидова и органа карлице назад у главну циркулацију. Спољашња илијачна вена (СИВ) првенствено дренира доње екстремитете, док унутрашња илијачна вена (УИВ) дренира карличне органе, зидове, глутеални регион и перинеум. Све вене из карлице и доњег екстремитета углавном се одводе у доњу шупљу вену (ДШВ) и даље ка десној преткомори. Мањи крвни судови могу варирати од појединца до појединца, али су главни судови са анатомског аспекта врло константни код сваког појединца.

Јајнике и материцу дренирају и унутрашње илијачне и оваријалне вене (ОВ). УИВ пролази благо медијално и постериорно од унутрашње илијачне артерије, спајајући се са СИВ и формира заједничку илијачну вену (ЗИВ). Њене притоке су подељене на паријеталне и висцералне. Париеталне притоке су горња и доња глутеална, ишијадична, сакрална, узлазна лумбална и оптураторна вена. Висцералне притоке су унутрашњи пудендални, средњи хемороидни и везикопростатични плексуси код мушкараца и утерални, гонадни и везиковагинални плексуси код жена. Залисци се ретко налазе на унутрашњим илијачним венама (10% случајева на главном трупу и 9% на његовим притокама).

Оваријалне вене обезбеђују дренажу пампиниформног плексуса, мезосалпинкса, параметријума и грлића материце, формирајући богат анастомотски венски плексус са параоваријалним, утериним, везикалним, ректалним и вулварним плексусима. Два или три стабла формирају једну вену јајника на Л4, при чему се лева вена јајника дренира у леву бубрежну вену (ЛБВ), а десна вена јајника код већине жена директно под оштрим углом у антеро-латерални зид ДШВ, испод десне бубрежне вене (ДБВ). Код до 10% жена, десна вена јајника такође може да се увуче у ДБВ уместо у ДШВ. Студије су показале да нормалне вене јајника имају просечан пречник мањи од 5 мм. Залисци су присутни у овим венама, углавном у дисталној трећини. Залисци нису

dysmenorrhea, lumbar pain, frequent and urgent urination, and signs of dilated vulvar, perineal, gluteal superficial veins or varicosities of the lower extremities and hemorrhoids [1]. Chronic pelvic pain is not necessary for diagnosis, as in many patients the predominant symptom may be atypical superficial varicosities. In some women, superficial varicose veins may be the only sign of PVI. The prevalence of vulvar varicosities in patients with PVCS ranges from 24–40%. Up to 80% of patients with pelvic venous dilation may exhibit varying degrees of associated venous insufficiency of the lower extremities [2].

The complexity of the problem lies in the fact that different symptoms can occur at the same degree of PVI, just as the same symptoms may appear at different degrees of PVI. Chronic pelvic pain in women can arise from various causes, including endometriosis, adhesions, fibroids, adenomyosis, genital organ prolapse, malignancies, and many other causes; very often, in the absence of an explanation for the pain, chronic pain is attributed to psychosomatic disorders.

Due to the nonspecific symptomatology, PVCS is often unrecognized and underdiagnosed. Factors that exacerbate pelvic pain, as described in the literature, include prolonged periods of standing, walking, or sitting, as well as factors that increase intra-abdominal pressure, such as lifting and pregnancy. Pain generally worsens during the day, as well as before and in the first days of menstruation, and decreases when lying down.

Pain also increases during and after sexual intercourse. Osman et al. reported that dyspareunia due to endometriosis is typically associated with deep penetration, whereas pain caused by PVCS usually worsens with sexual activity, producing a pulsating pain after intercourse [3].

Urinary symptoms may occur in PVCS due to perivesical varicosities, such as bladder irritability, urgency, or dysuria. Other manifestations of PVCS can include rectal discomfort, vulvar swelling, vaginal discharge, persistent genital arousal, and nonspecific gastrointestinal symptoms such as bloating and nausea. Chronic pelvic pain and these additional symptoms negatively affect patients' quality of life, leading to a significantly higher incidence of depression, anxiety, and generalized lethargy in this group. [1].

***Anatomy***

The pelvic venous system is responsible for returning venous blood from the walls and organs of the pelvis back to the central circulation. The external iliac vein (EIV) primarily drains the lower extremities, whereas the internal iliac vein (IIV) drains the pelvic organs, pelvic walls, gluteal region, and perineum. All veins from the pelvis and lower extremities generally converge into the inferior vena cava (IVC) and proceed to the right atrium. Smaller vessels can vary between individuals, but the major vessels are anatomically consistent.

The ovaries and uterus are drained by both the internal iliac and ovarian veins (OV). The IIV runs slightly medial and posterior to the internal iliac artery, joining the EIV to form the common iliac vein (CIV). Its tributaries are divided into parietal and visceral groups. Parietal tributaries include the superior and inferior gluteal, sciatic, sacral, ascending lumbar, and obturator veins. Visceral tributaries include the internal pudendal, middle hemorrhoidal, and vesicoprostatic plexuses in men, and the uterine, gonadal, and vesicovaginal plexuses in women. Valves are rarely present in the internal iliac veins (10% of cases in the main trunk and 9% in its tributaries).

The ovarian veins drain the pampiniform plexus, mesosalpinx, parametrium, and cervix, forming a rich anastomotic venous network with the paraovarian, uterine, vesical, rectal, and vulvar plexuses. Two or three branches form a single ovarian vein at the level of L4, with the left ovarian vein draining into the left renal vein (LRV), and the right ovarian vein in most

присутни у 15% случајева у левој ОВ и 6% у десној ОВ. Када су залисци присутни, они су инкомпетентни у 40% случајева лево и 35% десно [1]. Левострана доминација ПВКС-а може се објаснити претходно наведеним чињеницама као и тиме да је лева ОВ дужа од десне ОВ, што отежава дренирање у усправном положају. Поред тога, лева ОВ може бити компримована сигмоидним колоном који се налази на левој страни током опстипације. Ипак, треба напоменути да је венска дренажа карлице сложена и да венска анатомија може да варира између пацијената [5].

***Етиологија и патофизиологија***

Етиологија ПВКС и даље остаје слабо схваћена и сматра се да многи фактори доприносе патогенези. ПВИ може бити узрокована комбинацијом више фактора: генетском предиспозицијом, анатомским абнормалностима, хормонским факторима, дисфункционалним залисцима, опструкцијом венског тога од стране суседних структура и оштећењем зидова вена.

Многе студије указују на повезаност проширених вена и генетике а према неким извештајима и до 50% проширених вена може бити повезано са генетиком.

Могу постојати неке урођене абнормалности зида вена које узрокују њихово ширење, што доводи до дисфункције залистака.

Хормонски фактори такође играју важну улогу у развоју ПВКС. Естроген изазива повећано лучење азотног оксида. Ово резултира повећаном дилатацијом и слабљењем вена, што узрокује већи стрес на залисцима. Прогестерон својом активношћу такође слаби венске залиске у венама карлице. Трудноћа се сматра једном од главних опасности за ПВКС. Пре свега због појачаног обима циркулације у венама карлице, повећаног протока кроз оваријалне вене чак и до 60 пута као и повећаног интраабдоминалног притиска изазваног дејством трудне материце који додатно повећава рефлукс кроз вене јајника. Естрадиол изазива дилатацију вена током трудноће и доводи до већег стреса на залиске и у крајњем исходу долази до хроничне венске инсуфицијенције. Коришћење вазоконстриктора у терапијске сврхе је показало одређену ефикасност у ублажавању симптома ПВКС повећањем венског протока кроз компресију, што подржава хормонску теорију. Поред тога, симптоми обично потпуно нестају након менопаузе.

Без обзира што су залисци углавном присутни у дисталним деловима главних стабала оваријалних вена (у око 85% случајева), они су инкомпетентни у 40% случајева у левој и 35% случајева у десној оваријалној вени [6]. Механизми помоћу којих венски залисци постају инкомпетентни нису прецизно дефинисани. С једне стране, може постојати примарна промена у структури залиска, које доводи до пропуштања, прогресивног рефлукса и на крају проширење вена. С друге стране, може постојати основна структурна неисправност-неправилност у зиду вена које доводе до проширених вена које доводе до тога да залисци постану изобличени и нефункционални [5].

ПВКС такође може бити резултат опструкције одлива крви из оваријалних вена. Најчешћи узрок опструкције је компресија леве реналне артерије између горње мезентеричне артерије и абдоминалне аорте, стање познато као као синдром Крцка орашчића (*Nutcracker sydrome*). Меј Тарнеров синдром (*May-Thurner sydrome*), је још један узрок опструкције. То је стање у коме је лева заједничка илијачна вена компримована десном заједничком илијачном артеријом. Ова компресија понекад може довести и до дубоке венске тромбозе. Неправилан положај материце са савијањем јајника може бити узрок опструкције али доста ретко. Поред тога ендометриотична жаришта, миоми, постхируршке или инфективне адхезије, хиперваскуларни тумори карлице, гестацијске трофобластне неоплазме, тумори јајника као и мезентерични тумори такође могу изазвати компресију вена. Без обзира на етиологију, крајњи резултат опструкције је развој бројних рефлуксних варикозитета, унакрсних венских колатерала и болне венске конгестије [1].

Продужена венска дилатација у проширеним венама у ПВИ изазива упалу која даље оштећује зидове судова изазивајући додатно слабљење и дилатацију вена и раст рефлукса. Венска хипертензија појачава експресију матрикс металопротеиназе што промовише деградацију колагена, еластина и ендотела,

women draining directly at an acute angle into the anterolateral wall of the IVC, below the right renal vein (RRV). In up to 10% of women, the right ovarian vein may drain into the RRV instead of the IVC. Studies have shown that normal ovarian veins have an average diameter of less than 5 mm. Valves are present, mainly in the distal third of the vein. Valves are absent in 15% of left OVs and 6% of right OVs. When present, valves are incompetent in 40% of cases on the left and 35% on the right [1].

The left-sided predominance of PVCS can be explained by these anatomical features, as well as by the fact that the left ovarian vein is longer than the right, which impedes drainage in the upright position. Additionally, the left ovarian vein may be compressed by the sigmoid colon during constipation. Nonetheless, it should be noted that pelvic venous drainage is complex and venous anatomy can vary among patients. [5].

### *Etiology and Pathophysiology*

The etiology of Pelvic Venous Congestive Syndrome (PVCS) remains poorly understood, and it is considered that multiple factors contribute to its pathogenesis. Pelvic venous insufficiency (PVI) can result from a combination of factors, including genetic predisposition, anatomical abnormalities, hormonal influences, valve dysfunction, obstruction of venous outflow by adjacent structures, and damage to the vein walls.

Many studies have indicated a connection between varicose veins and genetics, with some reports suggesting that up to 50% of varicose veins may have a genetic component. Congenital abnormalities of the vein wall may also exist, causing dilation and subsequent valve dysfunction.

Hormonal factors play a significant role in the development of PVCS. Estrogen increases nitric oxide production, resulting in venous dilation and weakening, which increases stress on the valves. Progesterone also contributes to weakening venous valves in the pelvic veins. Pregnancy is considered one of the major risk factors for PVCS due to increased circulatory volume in the pelvic veins, elevated flow through the ovarian veins (up to 60-fold), and increased intra-abdominal pressure caused by the gravid uterus, which further exacerbates ovarian vein reflux. Estradiol-induced venous dilation during pregnancy increases valve stress, ultimately leading to chronic venous insufficiency. The therapeutic use of vasoconstrictors has shown some efficacy in alleviating PVCS symptoms by increasing venous flow through compression, supporting the hormonal theory. Additionally, symptoms typically resolve completely after menopause.

Although valves are generally present in the distal segments of the main ovarian vein trunks (about 85% of cases), they are incompetent in 40% of cases on the left and 35% on the right ovarian vein [6]. The mechanisms by which venous valves become incompetent are not precisely defined. On one hand, there may be a primary change in valve structure leading to leakage, progressive reflux, and subsequent vein dilation. On the other hand, a primary structural abnormality in the vein wall may cause venous dilation, which distorts the valves and renders them nonfunctional [5].

PVCS can also result from obstruction of blood outflow from the ovarian veins. The most common cause of obstruction is compression of the left renal vein between the superior mesenteric artery and the abdominal aorta, known as Nutcracker syndrome. May-Thurner syndrome is another cause of obstruction, where the left common iliac vein is compressed by the right common iliac artery. This compression can sometimes lead to deep vein thrombosis. Abnormal uterine positioning with ovarian torsion can rarely cause obstruction. Additionally, endometriotic lesions, fibroids, postsurgical or infectious adhesions, hypervascular pelvic tumors, gestational trophoblastic neoplasms, ovarian tumors, and mesenteric tumors can also compress veins. Regardless of etiology, the final result of obstruction is the development of numerous refluxing varicosities, cross-

нарушавајући контролу васкуларне напетости [7]. Ово промовише даље оштећење ендотелних ћелија и упалу.

Иако венска дистензија генерално не би требало да изазива бол, конгестија и истезање вена јајника и карлице могу активирати рецепторе за бол унутар венских зидова. Дилатација вена доводи до активације ноцицептора који су повезани са Ц аферентним влакнима који имају малу брзину проводљивости и посредују настанку тупог и пекућег бола [2].

Венска дилатација и запаљење изазива ослобађање супстанце П и пептида повезаног са геном калцитонина (ППГК), што даље додатно шири суд и повећава пропустљивост васкуларног зида. Истовремено се ослобађају цитокини који повећавају упалу и активност ноцицептора [8].

Поткрепљујући доказ да дилатација карличних вена доводи до активација рецептора за бол је да су габапентин и амитриптилин, стандард у третману неуропатског бола, ефикаснији од опиоидних или нестероидних аналгетика за ублажавање болова у карлици [9].

**Дијагноза**

Дијагноза ПВКС и даље представља велики изазов, с обзиром на недостатак универзално прихваћених критеријума у дијагностичким имиџинг модалитетима као и због његове мултиформности. Пацијенти са ПВКС се обично прво обрате лекару опште праксе и/или гинекологу у примарној здравственој заштити пре него што се упуте на даља испитивања и консултације. Када се искључе чешћи узроци хроничног карличног бола, укључујући ендометриозу, инфламаторну болест карлице, интерстицијски циститис и фиброиде, први корак је обично ултразвучни преглед карлице (УЗ) за визуализацију крвних судова [1].

Различите номенклатуре су коришћене за разноврсну клиничку презентацију пелвичне венске инсуфицијенције. Корак ка побољшању разумевања ове болести би могао бити недавно успостављена класификација „Симптоми-Варикси-Патофизиологија" (СВП) за процену карличних венских поремећаја од стране Међународне радне групе сазване од стране Америчког удружена за вене и лимфатике. Иако ова класификација делује сложено за примену у свакодневој пракси, она би могла помоћи у прецизнијем дијагностиковању, бољем селектовању пацијенткиња за терапијски третман и да се добију хомогенији узорци за будућа истраживања [10].

За дијагностиковање се могу користити следеће имиџинг методе: ултразвук (УЗ), компјутеризована томографија (ЦТ), магнетна резонанца (МР) као неинвазивне методе и венографија (ВГ) као инвазивна метода.

**Ултразвук карлице је обично метода прве линије код пацијената са сумњом на ПВКС.** Ултразвуком се процењује анатомија карличних структура а коришћењем доплер модова омогућена је визуализација крвних судова и евалуација протока у њима. Ултразвук може бити трансвагинални, трансабдоминални или трансперинеални .Трансвагинални ултразвук (ТВУ) може боље искључити друге гинеколошке проблеме, пружа бољу визуализацију венских плексуса карлице и омогућава динамички испитивање протока крви кроз вијугаве вене карлице али трансабдоминални и трансперинеални УЗ омогућавају бољу визуализацију суда на дужем току, нпр. оваријалне вене. Ултразвук омогућава и снимање пацијената у стојећем положају или док изводе Валсалвин маневар са наглашавањем венског пуњења и омогућавањем боље визуализације карличних варикозитета [2,5].

У ултразвучној процени, постоје различити предложени параметри који се могу испитивати, а то су унутрашњи пречник највеће карличне вене (десна и лева страна), максимални пречник највећег венског плексуса (десна и лева страна), дилатација и ниска брзина или обрнути ток крвотока у оваријалним венама приликом Валсалве, проширење лучних вена (vv. arcuate) у миометријуму, присуство укрштања вена као и максимални дијаметар укрштених вена у миометријуму, запремину материце, запремину десног и левог јајника, присуство полицистичних јајника (ПЦО).

Гранична вредност за проширење оваријалних вена је још увек контроверзна тема, а различити аутори је утврђују негде између 5 и 8 мм. Према Парк и др. позитивна

venous collaterals, and painful venous congestion. [1].

Prolonged venous dilation in varicose veins in PVI induces inflammation, which further damages the vessel walls, causing additional weakening and dilation of the veins and increasing reflux. Venous hypertension enhances the expression of matrix metalloproteinases, promoting the degradation of collagen, elastin, and endothelium, thereby impairing vascular tone regulation [7]. This process leads to further endothelial damage and inflammation.

Although venous distension generally should not cause pain, congestion and stretching of the ovarian and pelvic veins can activate pain receptors within the venous walls. Venous dilation leads to activation of nociceptors connected to C-afferent fibers, which have slow conduction velocities and mediate the sensation of dull, burning pain [2].

Venous dilation and inflammation also trigger the release of substance P and calcitonin gene-related peptide (CGRP), which further dilate the vessels and increase vascular wall permeability. Simultaneously, cytokines are released, enhancing inflammation and nociceptor activity [8].

Supporting evidence that dilation of pelvic veins activates pain receptors comes from clinical observations that gabapentin and amitriptyline—standard treatments for neuropathic pain—are more effective than opioids or nonsteroidal analgesics in alleviating pelvic pain. [9].

**Diagnosis**

The diagnosis of Pelvic Venous Congestion Syndrome (PVCS) remains challenging due to the lack of universally accepted criteria in imaging modalities and its heterogeneous presentation. Patients with PVCS typically first consult a general practitioner and/or gynecologist in primary care before being referred for further investigations and specialist consultation. Once more common causes of chronic pelvic pain—including endometriosis, pelvic inflammatory disease, interstitial cystitis, and fibroids—are excluded, the first diagnostic step is usually pelvic ultrasound (US) to visualize the blood vessels [1].

Various nomenclatures have been used to describe the diverse clinical presentation of pelvic venous insufficiency. A step toward better understanding of this condition is the recently established “Symptoms-Varices-Pathophysiology” (SVP) classification for assessing pelvic venous disorders, proposed by the International Working Group convened by the American Vein and Lymphatic Society. Although this classification may seem complex for routine clinical practice, it could help in more precise diagnosis, better selection of patients for therapeutic intervention, and generation of homogeneous samples for future research [10].

Imaging methods for diagnosis include non-invasive techniques such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), as well as invasive venography (VG).

Pelvic ultrasound is generally the first-line method for patients suspected of having PVCS. Ultrasound assesses pelvic anatomy and, using Doppler modes, allows visualization of blood vessels and evaluation of blood flow. Ultrasound can be performed transvaginally, transabdominally, or transperineally. Transvaginal ultrasound (TVUS) better excludes other gynecological conditions, provides improved visualization of pelvic venous plexuses, and allows dynamic assessment of blood flow through tortuous pelvic veins. Transabdominal and transperineal ultrasound, on the other hand, allow better visualization of longer vessels, such as the ovarian veins. Ultrasound can also be performed with the patient standing or performing the Valsalva maneuver, which accentuates venous filling and improves visualization of pelvic varices [2,5].

предиктивна вредност као гранични пречник леве оваријалне вене била је 71,2% на 5 мм, 83,3% на 6 мм, 81,8% на 7 мм и 75,8% на 8 мм [11].

Rocio Garcia-Jimenez и др. су дизајнирали ултразвучни предиктивни модел за идентификацију ПВКС заснован на присуству карличне вене или венског плексуса димензије од 8 мм или веће, идентификованих са ТВУ, који може предвидети 79% пацијената са ПВКС, са добрим вредностима сензитивности (86,05%) и специфичности (66,67%). С обзиром на његову једноставност, која укључује само један параметар, овај модел се чини изводљивом алтернативом, за разлику од предиктивних модела који су претходно предлагани [12]. Labropoulos и др су 2017. године известили о стандардизацији и техници примене ултразвука у дијагностици ПВКС трансабдоминалним приступом [13].

Компјутерска томографија (ЦТ) омогућава снимање у попречним пресецима и прецизну анатомску визуализацију. Магнетна резонанца (МР) карлице може да обезбеди одличан квалитет слике и високу резолуцију и за разлику од ЦТ-а, МР не укључује употребу зрачења и може се безбедније користити код жена у репродуктивној доби. Дијагностички критеријуми за ЦТ и МРИ које препоручују Coakley и др. укључују постојање најмање четири ипсилатералне кривудаве параутерине вене различитог калибра, најмање једну вену пречника >4 мм или пречник оваријалне вене >8 мм [14]. ЦТ и МР са контрастом или без контраста обезбеђују добру осетљивост у дијагностици венске инсуфицијенције. Osman и др. су известили осетљивост ЦТ-а од 94,8% и МР од 96% [15].

Информације у вези са протоком кроз вене у МР могу се обезбедити коришћењем МР техника као што су мапирања брзине фазног контраста (Phase Contrast MRI) или Time Resolved MRA које пружају тачне информације, да ли је проток у оваријалној вени антероградан или ретроградан. Yang и др. су упоредили Time Resolved MRA са конвенционалном венографијом. Резултати су показали да је Time Resolved MRA одличан неинвазивни дијагностички алат за ПВИ, јер није било значајне разлике између конвенционалне венографије и Time Resolved MRA за одређивање нивоа оваријалног венског рефлукса [16].

Лапароскопија није добра метода у детекцији варикозитета карлице и она је негативна код 80%–90% пацијената са ПВКС јер захтева Тренделенбург-ов положај и инсуфлацију угљен-диоксида са повећањем интраперитонеалног притиска, који компримује (и често прикрива) варикозитет карлице. Међутим, лапароскопија омогућава визуализацију других узрока хроничног карличног бола [2].

Транскатетерска венографија и даље остаје златни стандард за дијагнозу ПВКС. Пошто се ради о инвазивној процедури, требало би је резервисати за пацијенте код којих претходни налази неинвазивних имиџинг метода нису коначни или код пацијената код којих се планира интервентна терапија емболизацијом [15]. Венографија усмерена катетером се изводи увођењем катетера од југуларне, брахијалне или феморалне вене до реналне, оваријалне, заједничке илијачне и унутрашње илијачне вене и убризгавањем контрастног средства. Ова техника може да мери градијенте притиска, што пружа драгоцене информације о степену патологије карличних вена, и може да пружи морфолошке информације о венама. Изводи се у амбулантном режиму, без потребе за хоспитализацијом. Главна предност ове дијагностичке процедуре је у томе што је могуће извршити третман у истом поступку. Главни протокол почиње катетеризацијом леве бубрежне вене, са истовременим мерењем градијента притиска за испитивање синдрома орашчића. Затим се катетер помера у леву илијачну вену, да би се урадило исто за Мај Тарнеров синдром. Након тога се истражују оваријалне вене и на крају унутрашње илијачне вене [17].

Венографски дијагностички критеријуми за некомпетентне карличне вене укључују пречник оваријалне вене >10 мм; конгестија оваријалних, пелвичних, вулвовагиналних вена и ретроградно пуњење [5].

**Третман**

Конзервативни третман медикаментима за ПВКС је ограничен с обзиром да још увек недостају подаци о дугорочној ефикасности.

Ultrasound parameters that can be evaluated include: internal diameter of the largest pelvic vein (right and left), maximum diameter of the largest venous plexus (right and left), dilation and low velocity or reversed flow in the ovarian veins during Valsalva, enlargement of arcuate veins (vv. arcuate) in the myometrium, presence of crossed veins, maximum diameter of crossed veins in the myometrium, uterine volume, volume of the right and left ovary, and presence of polycystic ovaries (PCO).

The threshold for ovarian vein dilatation remains controversial, with different authors defining it between 5 and 8 mm. According to Park et al., the positive predictive value for a threshold diameter of the left ovarian vein was 71.2% at 5 mm, 83.3% at 6 mm, 81.8% at 7 mm, and 75.8% at 8 mm. [11].

Rocio Garcia-Jimenez et al. designed an ultrasound predictive model for identifying PVCS based on the presence of a pelvic vein or venous plexus measuring 8 mm or more, identified via transvaginal ultrasound (TVUS). This model was able to predict 79% of patients with PVCS, with good sensitivity (86.05%) and specificity (66.67%). Given its simplicity, relying on a single parameter, this model appears to be a feasible alternative compared to previously proposed predictive models [12]. Labropoulos et al. (2017) reported on the standardization and technique of ultrasound application in PVCS diagnosis using a transabdominal approach [13].

Computed tomography (CT) allows imaging in cross-sections and precise anatomical visualization. Magnetic resonance imaging (MRI) of the pelvis provides excellent image quality and high resolution, and unlike CT, does not involve radiation, making it safer for women of reproductive age. Diagnostic criteria for CT and MRI proposed by Coakley et al. include the presence of at least four ipsilateral tortuous parauterine veins of varying calibers, at least one vein with a diameter >4 mm, or an ovarian vein diameter >8 mm [14]. Both contrast-enhanced and non-contrast CT and MRI provide good sensitivity in diagnosing venous insufficiency. Osman et al. reported a sensitivity of 94.8% for CT and 96% for MRI [15].

Flow information in the veins can be obtained using MRI techniques such as phase-contrast velocity mapping (Phase Contrast MRI) or Time-Resolved MRA, which provide accurate information on whether flow in the ovarian vein is antegrade or retrograde. Yang et al. compared Time-Resolved MRA with conventional venography, showing that Time-Resolved MRA is an excellent non-invasive diagnostic tool for pelvic venous insufficiency, with no significant difference compared to conventional venography in determining the level of ovarian venous reflux [16].

Laparoscopy is not effective in detecting pelvic varices and is negative in 80–90% of PVCS patients because it requires Trendelenburg positioning and $CO_2$ insufflation, which increases intra-abdominal pressure and compresses (often masking) pelvic varices. However, laparoscopy allows visualization of other causes of chronic pelvic pain [2].

Transcatheter venography remains the gold standard for PVCS diagnosis. As an invasive procedure, it should be reserved for patients whose non-invasive imaging findings are inconclusive or for those planned for interventional embolization therapy [15]. Catheter-directed venography is performed by inserting a catheter via the jugular, brachial, or femoral vein to the renal, ovarian, common iliac, and internal iliac veins, followed by contrast injection. This technique allows measurement of pressure gradients, providing valuable information about the severity of pelvic venous pathology, as well as morphological assessment of the veins. The procedure is usually performed on an outpatient basis without hospitalization. A key advantage is that treatment can be performed in the same session. The main protocol begins with catheterization of the left renal vein, simultaneously measuring the pressure gradient to assess Nutcracker syndrome. The catheter is then moved to the left iliac vein to

Хормонске терапије које инхибирају функцију јајника, као што су медроксипрогестерон ацетат (МПА) и агонисти гонадотропин-ослобађајућег хормона (ГнРХ), показале су извесну ефикасност, али је терапија била праћена бројним нежељеним ефектима. Употреба дихидроерготамина је показала извесну ефикасност у смањењу бола али је ефикасност била пролазна уз појаву нежељених ефеката. Такође, нестероидни антиинфламаторни лекови могу да смање симптоме, али не доприносе излечењу [2].

Микронизована пречишћена флавоноидна фракција (МПФФ), веноактивни лек, истраживали су Simsek и др., Tsukanov и др. и Gavrilov и др. Сви истраживачи су показали да 1000 мг МПФФ дневно смањује тежину карличних симптома као што су бол, тежина и отицање великих усана услед проширених вена карлице [18,19,20]. Поред тога, Гаврилов и др. показали су да двострука доза МПФФ-а (1000 мг два пута дневно) у првом месецу лечења обезбеђује брже решавање симптома [21].

Компресија је једна од терапијских опција конзервативног третмана ПВКС. У студији коју су спровели Гаврилов и сар. Компресијски шорц коришћен 2 недеље смањио је хронични бол у карлици, диспареунију и нелагодност код 81,3% пацијената. Такође су смањили тежину и отицање ногу. Међутим, они нису имали утицаја на клиничке симптоме проширених вена вулве. У групи која је користила еластичне чарапе није примећено клиничко побољшање или побољшање венске дренаже [22].

Неконзервативни третман би подразумевао хируршко лечење као и минимално инвазивну ендоваскуларну терапију. Раније студије су извештавале о ресекцији вене левог јајника, хистеректомији са унилатералном или билатералном аднексектомијом као методама лечења ПВКС. Међутим, оне су имале велику стопу рецидива, резидуална бол се појављивала доста често а повезане су са дужим боравком у болници и већим морталитетом у поређењу са ендоваскуларном терапијом.

У рандомизованој контролној студији коју су спровели Chung и др. емболизација вене јајника била је значајно ефикаснија од хистеректомије са унилатералном или билатералном салпингоофоректомијом 12 месеци након третмана [23].

Први опис емболизације као третмана за ПВКС објавио је 1993. године Едвардс. Према Друштву за васкуларну хирургију и Америчком венском форуму, емболизација се препоручује са нивоом доказа 2Б за лечење ПВКС [17]. Емболизација се обично изводи након неуспешног медикаментног третмана али се све више користи као примарни третман за ПВКС. Индикације за емболизацију се разликују у различитим публикацијама али се генерално емболизација препоручује код жена са хроничним пелвичним болом и/или диспареунијом, код жена са тешким лабијалним, перинеалним варикозитетима или вариксима доњих екстремитета уз обавезну доказану пелвичну венску инсуфицијенцију, обично потврђену венографијом. Због слабог препознавања ове болести, не постоји дефинитиван протокол ендоваскуларног лечења ПВКС. И техника, као што је место интраваскуларног приступа, и материјали који се користе за емболизацију као што су склерозанти, калемови и чепови, варирају у публикацијама на ову тему [2]. Трајно клиничко побољшање након емболизације креће се у различитим студијама од 47 до 100% [2]. Још увек се води дебата о томе колико вена треба да буде емболисано. Разлика није статистички значајна у поређењу унилатералне и билатералне емболизације. Неки клиничари спроводе само једнострану емболизацију вена јајника, док други спроводе потпуну емболизацију [2].

Када је присутна стеноза, која представља хемодинамски значајан проблем, треба предузети отклањање опструкције. У том случају се може стентирати лева заједничка илијачна вена код Мај Тарнеровог синдрома или лева бубрежна вена код синдрома орашчића као и свако друго место опструкције карличних вена доступно катетеру. Стентирање леве бубрежне вене је повезано са високим ризиком од миграције стента у шупљу вену и срце због кратке дужине вене и промене пречника вене када пацијент промени положај или изврши Валсалвин маневар [24]. Највећи ризик од неуспеха ендоваскуларног стентирања је

evaluate May-Thurner syndrome. Subsequently, the ovarian veins are assessed, followed by the internal iliac veins [17].

Venographic diagnostic criteria for incompetent pelvic veins include an ovarian vein diameter >10 mm; congestion of ovarian, pelvic, vulvovaginal veins; and retrograde filling. [5].

**Treatment of Pelvic Venous Congestion Syndrome (PVCS)**

Conservative (Medical) Treatment

Medical management of PVCS is limited, as long-term efficacy data are lacking. Hormonal therapies that inhibit ovarian function, such as medroxyprogesterone acetate (MPA) and gonadotropin-releasing hormone (GnRH) agonists, have shown some efficacy, but their use is associated with multiple side effects. Dihydroergotamine has demonstrated temporary pain relief, but its effects are transient and accompanied by adverse events. Nonsteroidal anti-inflammatory drugs (NSAIDs) may alleviate symptoms but do not address the underlying condition [2].

Micronized purified flavonoid fraction (MPFF), a venoactive drug, has been investigated by Simsek et al., Tsukanov et al., and Gavrilov et al. All studies showed that 1000 mg of MPFF daily reduces the severity of pelvic symptoms such as pain, heaviness, and vulvar swelling due to pelvic varices [18,19,20]. Gavrilov et al. also demonstrated that doubling the dose (1000 mg twice daily) in the first month accelerates symptom resolution [21].

Compression garments are another conservative treatment option. In a study by Gavrilov et al., wearing compression shorts for 2 weeks reduced chronic pelvic pain, dyspareunia, and discomfort in 81.3% of patients. They also reduced leg heaviness and swelling. However, there was no effect on clinical symptoms of vulvar varices. Elastic stockings did not show clinical improvement or enhanced venous drainage [22].

Non-conservative treatment includes surgical intervention and minimally invasive endovascular therapy. Earlier surgical approaches, such as left ovarian vein resection or hysterectomy with unilateral or bilateral adnexectomy, were associated with high recurrence rates, residual pain, longer hospital stays, and higher morbidity compared to endovascular approaches.

In a randomized controlled trial by Chung et al., ovarian vein embolization was significantly more effective than hysterectomy with unilateral or bilateral salpingo-oophorectomy 12 months post-treatment [23].

The first report of embolization as a treatment for PVCS was published by Edwards in 1993. According to the Society for Vascular Surgery and the American Venous Forum, embolization is recommended with a 2B level of evidence for PVCS treatment [17]. Embolization is usually performed after unsuccessful medical therapy but is increasingly used as a primary treatment. Indications generally include women with chronic pelvic pain and/or dyspareunia, severe labial or perineal varices, or lower limb varices, with confirmed pelvic venous insufficiency, typically verified by venography.

There is no standardized protocol for endovascular PVCS treatment. Techniques, vascular access sites, and embolic materials (sclerosants, coils, plugs) vary across publications [2]. Clinical improvement after embolization ranges from 47% to 100% in different studies [2]. The debate continues over whether unilateral or bilateral embolization should be performed; some clinicians perform only unilateral ovarian vein embolization, while others perform complete bilateral embolization [2].

If a hemodynamically significant stenosis is present, it should be corrected. This may include stenting the left common iliac vein in May-Thurner syndrome or the left renal vein in Nutcracker syndrome, as well as any other catheter-accessible site of pelvic venous obstruction. Stenting of the left renal

оклузија стента, а трајање антитромботичке терапије после процедуре варира између студија [2].

Компликације перкутане емболизације су обично ретке и безопасне. То укључује алергијску реакцију, хематом на месту пункције, локални тромбофлебитис, перфорација крвног суда, миграцију емболичког средства као и понављање симптома. Симптоми ПВКС-а се могу поново појавити након емболизације вене јајника из других притока у венској мрежи. Постемболизацијски синдром се може јавити код 20% пацијената. Карактерише се појачаним болом у карлици, хипертермијом и осетљивошћу око емболизоване вене, а обично се повлачи применом НСАИЛ-а. Потенцијално опасна компликација може бити миграција спирале или васкуларног чепа у плућну артерију. Међутим, обично се успешно уклања ендоваскуларно [2].

## ЗАКЉУЧАК

ПВКС је чест узрочник хроничног пелвичног бола код жена али се овај синдром због недовољног познавања често не препознаје и остаје недијагностикован. Симптоми могу бити неспецифични и често се потцењују. Дијагностика ПВКС је веома изазовна, тешка али и једнако важна због спровођења одговарајућег и циљаног лечења. Још увек недостају глобално прихваћени дијагностички алгоритми који омогућавају објективну дијагнозу. С обзиром да се највећи део пацијенткиња са хроничних пелвичним болом иницијално обрати лекарима опште праксе или гинеколозима, важно је да се у одсуству других узрока увек помишља и на овај синдром. Такође би била корисна додатна едукација гинеколога у примени ултразвука у дијагностици ПВИ и упознавање са дијагностичким критеријумима, с обзиром да је ултразвучни преглед метода првог избора у дијагностици ПВКС. Такође постоји потреба за валидираним имиџинг дијагностичким критеријумима.

У погледу лечења, чини се да је ендоваскуларна емболизација ефикасан метод али су потребна будућа рандомизована испитивања у циљу одређивања јасних протокола у управљању емболизацијом.

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vein carries a high risk of migration to the vena cava and heart due to the vein's short length and diameter changes during posture changes or Valsalva maneuvers [24]. The main risk of endovascular stenting failure is stent occlusion. Duration of post-procedural antithrombotic therapy varies between studies [2].

Complications are generally rare and minor, including allergic reactions, puncture site hematoma, local thrombophlebitis, vessel perforation, embolic migration, and recurrence of symptoms. PVCS symptoms may recur after ovarian vein embolization due to reflux from other venous tributaries. Post-embolization syndrome occurs in approximately 20% of patients and is characterized by increased pelvic pain, low-grade fever, and tenderness around the embolized vein, usually managed with NSAIDs. A potentially serious complication is migration of the coil or vascular plug to the pulmonary artery, which is typically successfully retrieved endovascularly. [2].

## CONCLUSION

Pelvic venous congestion syndrome (PVCS) is a common cause of chronic pelvic pain in women, but due to insufficient awareness, this syndrome is often unrecognized and remains undiagnosed. The symptoms can be nonspecific and are frequently underestimated. Diagnosing PVCS is very challenging and complex, yet equally important for implementing appropriate and targeted treatment. Globally accepted diagnostic algorithms that allow for an objective diagnosis are still lacking. Considering that most patients with chronic pelvic pain initially consult general practitioners or gynecologists, it is important to always consider this syndrome in the absence of other causes. Additional education of gynecologists in the use of ultrasound for diagnosing pelvic venous insufficiency (PVI) and familiarity with diagnostic criteria would also be beneficial, as ultrasound is the first-line method in PVCS diagnosis. There is also a need for validated imaging diagnostic criteria.

Regarding treatment, endovascular embolization appears to be an effective method; however, future randomized studies are needed to establish clear protocols for managing embolization..

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# TORZIJA JAJNIKA - pregledni rad

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**Sažetak:**Najveći broj torzija jajnika viđa se u reproduktivnom periodu, negde oko 71%, ali se javlja i kodfetusa i neonatusa, premanarhalnih devojčica, kod trudnica kao i kod žena u postmenopauzi. Dok je prava incidenca torzije ipak nepoznata, podaci govore da je torzija uzrok 2,7% hirurških intervencija, pa spada u peto najčešće stanje koje zahteva urgentnu operaciju. Da bi smo razumeli kako dolazi do torzije, moramo razumeti anatomiju potpornih veza materice i jajnika. Jajnik je mobilna stuktura sama po sebi, suspendovana za karlični zid infuldibulopelvičnim ligamentom i za matericu uteroovarijalnim ligamentom. Torzija nastaje usled parcijalne ili kompletne rotacije adneksalnih potpornih struktura, koja rezultira parcijarnom ili kompletnom opstrukcijom krvotoka u jajniku i dovodi do ovarijalne ishemije koja rezultira nekrozom, lokalnom hemoragijom i gubitkom funkcije. Torzija može nastati kod zena svih reproduktivnih starosnih dobi, ali najveći procenat ovarijalnih torzija dešava se ipak kod žena u reproduktivnom periodu sa prisutnim adneksalnim promenama poput funcionalnih cisti na jajniku i benignih tumora. Najčešći simptom je bol koji može biti praćen mučninom i povraćanjem. Fizičkim pregledom otkrivamo subfebrilnost, abdominalnu osetljivost, abdominalnu bol i pelvičnu adneksalnu masu. Postavljanje dijagnoze ovarijalne torzije najčešće zahteva kombinaciju anamnestičkih podataka, kliničkog pregleda i imidzing metoda. Rana dijagnoza i hirurška terapija su neophodne kako bi zaštitile ovarijalnu i tubarnu funkciju i prevenirale ozbiljniji morbiditet.
**Ključne reči:** Torzija jajnika, ovarijalna cista, benigni tumor, akutni abdomen

## UVOD

Najčešća stanja koja dovode do akutnog bola u ginekološkoj praksi predstavljaju ektopične trudnoće, pelvična inflamatorna bolest, ruptuirane ovarijalne ciste, torzija jajnika, torzija i degeneracija uterinog lejomioma i spontani pobačaji. Najveći broj torzija jajnika viđa se u reproduktivnom periodu, negde oko 71% [2], ali se javlja i kod fetusa i neonatusa, premanarhalnih devojčica, kod trudnica kao i kod žena u post menopauzi. Dok je prava incidenca torzije ipak nepoznata, podaci govore da je torzija uzrok 2,7% hirurških intervencija, pa spada u peto najčešće stanje koje zahteva urgentnu operaciju [2]. Druga studija nalazi da je 15% operisanih adneksalnih masa u torziji [3]. Postavljanje pravovremene dijagnoze od značaja je kako za očuvanje funkcije jajnika tako i za prevenciju sledstvenih komorbiditeta.

## PATOGENEZA I FAKTORI RIZIKA

Da bi smo razumeli kako dolazi do torzije, moramo razumeti anatomiju potpornih veza materice i jajnika. Jajnik je parni intraperitonealni organkoji ima dve osnovne uloge. Prva je produkcija polnih hormona, druga je stvaranje i oslobađanje oocite u toku procesa ovulacije i stvaranje žutog tela koje će obezbeđivati dovoljnu hormonsku stimulaciju najranijoj trudnoći do uspostavljanja funkcije same placente. Ono što je specifično i impresivno kod jajnika je da jajnik može uvećavati svoju zapreminu više stotina puta u toku reproduktivnog perioda žene, bez patoloških kliničkih manifestacija [4]. Jajnik je mobilna stuktura sama po sebi, suspendovana za karlični zid infuldibulopelvičnim ligamentom (koji se još naziva i suspenzorni ligament jajnika) kroz koji prolazi arterija ovarica i za matericu uteroovarijalnim ligamentom (ligamentum ovarium proprium) kroz koji prolazi ovarijalna grana arterije uterine. Osim suportivne uloge, ovi ligamenti imaju i nutritivnu ulogu jer kroz njih prolaze odgovarajući krvni sudovi za jajnik obezbeđujući jajniku dvostruku vaskularizaciju [5]. Torzija nastaje usled parcijalne ili kompletne rotacije adneksalnih potpornih struktura, pri


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# OVARIAN TORSION - review paper

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**Summary:** The largest number of ovarian torsions is seen in the reproductive period, around 71%, but it also occurs in fetuses and neonates, premenarchal girls, pregnant women, and postmenopausal women. Although the true incidence of torsion is still unknown, data show that torsion accounts for 2.7% of surgical interventions, making it the fifth most common condition requiring emergency surgery. To understand how torsion occurs, we must understand the anatomy of the supporting structures of the uterus and ovaries. The ovary is a mobile structure in itself, suspended from the pelvic wall by the infundibulopelvic ligament and attached to the uterus by the utero-ovarian ligament. Torsion occurs as a result of partial or complete rotation of the adnexal supporting structures, which leads to partial or complete obstruction of ovarian blood flow, resulting in ovarian ischemia, which leads to necrosis, local hemorrhage, and loss of function. Torsion can occur in women of all reproductive ages, but the highest percentage of ovarian torsions occurs in women in the reproductive period with adnexal changes such as functional ovarian cysts and benign tumors. The most common symptom is pain, which may be accompanied by nausea and vomiting. Physical examination may reveal low-grade fever, abdominal tenderness, abdominal pain, and a pelvic adnexal mass. Diagnosing ovarian torsion usually requires a combination of medical history, clinical examination, and imaging methods. Early diagnosis and surgical treatment are essential to preserve ovarian and tubal function and to prevent more serious morbidity..
**Keywords:** Ovarian torsion, ovarian cyst, benign tumor, acute abdomen

## INTRODUCTION

The most common conditions that lead to acute pain in gynecological practice include ectopic pregnancies, pelvic inflammatory disease, ruptured ovarian cysts, ovarian torsion, torsion and degeneration of uterine leiomyomas, and spontaneous miscarriages. The largest number of ovarian torsions is seen in the reproductive period, around 71% [2], but it also occurs in fetuses and neonates, premenarchal girls, pregnant women, and postmenopausal women. Although the true incidence of torsion is still unknown, data show that torsion accounts for 2.7% of surgical interventions, making it the fifth most common condition requiring emergency surgery [2]. Another study found that 15% of surgically treated adnexal masses are in torsion [3]. Timely diagnosis is important both for preserving ovarian function and for preventing subsequent comorbidities..

## PATHOGENESIS AND RISK FACTORS

To understand how torsion occurs, we must first understand the anatomy of the supporting structures of the uterus and ovaries. The ovary is a paired intraperitoneal organ with two primary functions: the production of sex hormones, and the development and release of the oocyte during ovulation, as well as the formation of the corpus luteum, which provides sufficient hormonal support to early pregnancy until placental function is established. What is specific and remarkable about the ovary is that it can increase its volume several hundred times during a woman's reproductive period without pathological clinical manifestations [4].

The ovary is a mobile structure, suspended from the pelvic wall by the infundibulopelvic ligament (also called the suspensory ligament of the ovary), through which the ovarian artery passes, and attached to the uterus by the utero-ovarian ligament (ligamentum ovarium proprium), through which the ovarian branch of the uterine artery passes. In addition to providing support, these ligaments also serve a nutritive role, as the blood vessels supplying the ovary run through them, ensuring dual vascularization of the ovary [5].

čemu se jajnik i tuba rotiraju i oko infundibulopelvičnog i oko uteroovarijalnog ligamenta, rezultirajući parcijarnom ili kompletnom opstrukcijom krvotoka u jajniku [6,7,8]. Tanki zidovi vena su podložniji potpunoj okluziji za razliku od mišićnih zidova krvnih sudova arterija. Kontinuirani arterijski protok bez venskog odvoda krvi dovodi do edema sa vidljivim uvećanjem jajnika. Dalja vaskularna kompresija dovodi do ovarijalne ishemije koja rezultira nekrozom, lokalnom hemoragijom i gubitkom funkcije [9]. Torkviraju se najčešće i jajnik i tuba istovremeno, retko, mada može doći i do torkvacije izolovano jajnika ili tube kada se govori o parcijarnoj torziji. Takođe su opisane torzije koje podrazumevaju uvrtanje paraovarijalne ili paratubarne ciste [6]. Desni jajnik češće podleže torziji od levog, moguće zbog toga što je desni uteroovarijlani ligament duži od levog, a samo prisustvo sigmoidnog kolona sprečava torziju sa te strane [8,10]. Takođe je moguća i bilateralna asinhrona torzija jajnika, ali ovi slučajevi su ipak retki [11]. Stepen izraženosti simptoma i morfoloških promena na jajniku zavisi dakle od vrste i stepena okluzije krvnih sudova jajnika. S obzirom na anatomsku građu i nalaze iz kliničke prakse mogli bi definisati rizikofaktore za adneksalnu torziju. Dakle, veća mobilnost jajnika udružena je sa torzijom koja se viđa kod dece pre menarhe jer imaju elenogirane infundibulopelvične veze. U ovoj populacionoj grupi više od polovine pacijentkinja ima morfološki normalne jajnike. Nakon ovog premenarhalnog perioda, ulaskom u pubertet, usled skraćivanja infundibulopelvičnih veza, i indcidenca ovarijalne torzije opada. Riziko faktor kod premenarhalnih devojčica može biti i prisustvo funkcionalne ciste ili benignog tumora najčešće teratoma i cistadenoma [12,13,14]. Takođe, opisane su torzije ciste jajnika još u fetalnom razdoblju (ultrazvučno se prati rast ciste i eventualno sekindarne promene u njimapoput hemoragije, kalcifikacija ili resorpcije) i kod neonatusa [15].

Najveći procenat ovarijalnih torzija dešava se ipak kod žena u reproduktivnom periodu sa prisutnim adneksalnim promenama poput funcionalnih cisti na jajniku i benignih tumora [8,9,16]. Maligni tumori i endometriotične ciste su retko uzrok ovarijlnoj torziji. U seriji prikaza slučajeva procenat ovarijalnih maligniteta je opisan ispod 3%. To je zato što ove promene izazivaju reakciju peritoneuma i stvaranje priraslica te fiksiraju tumefakt i na taj način onemogućavaju njegovo pomeranje [17]. Više od 80% pacijenata sa ovarijalnom torzijom ima ovarijalne mase preko 5 cm u prečniku. Veličina ovarijalne mase u korelaciji je sa rizikom torzije. U seriji od 87 studija slučajeva ovarijalne mase su opisivane u širokom rasponu od 3 do 30cm,prosečno oko 9,5cm [18]. Oko 10-22% torzija jajnika dešava se u trudnoći. Incidenca je nešto veća od 10-17 nedelje gestacije sa ovarijalnim masama većim od 4cm. Ovulacija, korpus luteum, indukcija ovulacije u tretmanu infertiliteta može prouzrokovati sindrom ovarijalne hiperstimulacije sa multiplim velikim cističnim promenama na jajnicima koje su sklone torziji. Sindrom policističnih jajnika takođe je rizik faktor [19]. Sa druge strane, kod pacijentkinja koje su imale neku hiruršku proceduru incidenca ovarijalne torzije je oko 2-15% i tada je u pitanju strangulacija ovarijalne peteljke oko prisutne priraslice.Opisana je irecidivantna torzija, odnosno, studije su pokazale da osobe koje su jednom imale torziju jajnika pod većim su rizikom za nastanak i istog – „salvage ovary“ i torzije drugog jajnika [8].

**Klinička prezentacija i klinički nalaz**

Ovarijalna torzija usled prisustva adneksalne mase izaziva različite simptome i znake i kliničku prezentaciju. Najčešći simptom je akutni i oštar bol u predelu donjeg abdomena ili male karlice praćen povraćanjem i mučninom (70%) kod žena u reproduktivnom dobu, u prisustvu adneksalne mase ili uvećanih jajnika kod PCOS ili ovarijalne hiperstimulacije, ili kod žena sa anamnezom predhodne torzije jajnika [17,18,20]. Neke pacijentkinje imaju samo osećaj mučnine bez povraćanja. Abdominalni bol je najčešće intermitentnog karaktera u vidu kolika sa postepenim pojačavanjem i smanjenjem bola, mada može biti i kontinuiran. Bol nastaje sekunadrno usled okluzije vaskularne peteljke i refraktaran je na analgetike. Iridira u ingvinalni predeo ili regiju boka. Premenarhalne pacijentkinje mogu prijavljivati difuzni bol u stomaku jer je njima teško da lokalizuju bol,i kod njih će najčešća simptomatologija biti povraćanje u odsustvu adneksalne promene - radi se o vagalnoj refleksnoj reakciji usled nadražaja peritoneuma. Kod neonatusa torzija će se manifestovati odbijanjem hrane, distenzijom stomaka, povraćanjem i iritabilnošću. Ovarijalna torzija bez infektivne patologije može biti

Torsion occurs as a result of partial or complete rotation of the adnexal supporting structures, during which the ovary and fallopian tube rotate around both the infundibulopelvic and utero-ovarian ligaments, resulting in partial or complete obstruction of ovarian blood flow [6,7,8]. The thin walls of the veins are more prone to complete occlusion compared to the muscular walls of arterial vessels. Continuous arterial inflow without venous outflow leads to edema with visible ovarian enlargement. Further vascular compression results in ovarian ischemia, leading to necrosis, local hemorrhage, and loss of function [9]. Most often, both the ovary and the fallopian tube undergo torsion simultaneously, although isolated torsion of the ovary or tube may occur, referred to as partial torsion. Torsion involving paraovarian or paratubal cysts has also been described [6]. The right ovary is more frequently affected than the left, possibly because the right utero-ovarian ligament is longer, and the presence of the sigmoid colon prevents torsion on the left side [8,10]. Bilateral asynchronous ovarian torsion is also possible, though rare [11]. The severity of symptoms and morphological ovarian changes depends on the type and degree of vascular occlusion. Based on anatomical features and clinical findings, we can define risk factors for adnexal torsion. Greater ovarian mobility is associated with torsion in premenarchal girls, who have elongated infundibulopelvic ligaments. In this population, more than half of patients have morphologically normal ovaries. After this premenarchal period, with puberty, the incidence of ovarian torsion decreases due to shortening of the infundibulopelvic ligaments. Risk factors in premenarchal girls may also include the presence of functional cysts or benign tumors, most commonly teratomas and cystadenomas [12,13,14].

Ovarian torsion has also been described in the fetal period (ultrasound may monitor cyst growth and secondary changes such as hemorrhage, calcifications, or resorption) and in neonates [15].

The highest percentage of ovarian torsions occurs in women of reproductive age with adnexal changes such as functional ovarian cysts and benign tumors [8,9,16]. Malignant tumors and endometriotic cysts are rarely the cause of ovarian torsion. In case series, the percentage of malignant ovarian tumors associated with torsion is reported to be below 3%. This is because such lesions cause peritoneal reactions and adhesions that fix the mass, thereby limiting its mobility [17]. More than 80% of patients with ovarian torsion have ovarian masses larger than 5 cm in diameter. The size of the ovarian mass correlates with the risk of torsion. In a series of 87 case studies, ovarian masses ranged widely from 3 to 30 cm, with an average of about 9.5 cm [18]. About 10–22% of ovarian torsions occur during pregnancy. The incidence is somewhat higher between the 10th and 17th weeks of gestation in the presence of ovarian masses larger than 4 cm. Ovulation, the corpus luteum, and ovulation induction in infertility treatment may cause ovarian hyperstimulation syndrome, with multiple large cystic ovarian changes that are prone to torsion. Polycystic ovary syndrome is also a risk factor [19]. On the other hand, in patients who have undergone a surgical procedure, the incidence of ovarian torsion is about 2–15%, typically due to strangulation of the ovarian pedicle around an existing adhesion. Recurrent torsion has also been described, and studies show that individuals who have experienced ovarian torsion once are at increased risk of developing torsion again—either of the same ovary ("salvage ovary") or of the contralateral ovary. [8].

**Clinical presentation and clinical findings**

Ovarian torsion caused by the presence of an adnexal mass results in a variety of symptoms, clinical signs, and presentations. The most common symptom is acute, sharp pain in the lower abdomen or pelvis, accompanied by nausea and vomiting (70%) in women of reproductive age, in the presence of an adnexal mass or enlarged ovaries in PCOS or ovarian hyperstimulation, or in women with a history of prior ovarian torsion [17,18,20]. Some patients experience only nausea without vomiting. Abdominal pain is most often intermittent, colicky in nature, with gradual intensification and relief, although it may also be continuous. The pain arises secondarily due to occlusion of the vascular pedicle and is refractory to analgesics. It may radiate to the inguinal region or flank. Premenarchal patients may report diffuse abdominal pain, as they often find it difficult to localize the discomfort. In this group, vomiting is the most common symptom in the absence of adnexal pathology—this represents a vagal reflex response due to peritoneal irritation. In neonates, torsion may present with

praćena i subfebrilnošću. Subfebrilnost se objašnjava nekrotičnim promenama u torkviranom jajniku, javlja se kod 2-20% pacijenata. Fizičkim pregledom otkrivamo subfebrilnost, abdominalnu osetljivost, abdominalnu bol i pelvičnu adneksalnu masu. Dijagnostički izazov dalje predstavlja i podatak da 30% pacijenata naročito u premanarhalnom periodu ne mora imati abdominalnu bol niti abdominalnu osetljivost [17,18,21-24].

**Dijagnoza**

Postavljanje dijagnoze ovarijalne torzije najčešće zahteva kombinaciju anamnestičkih podataka, kliničkog pregleda i imidzing metoda. Prvi pristup pacijentu je fizikalni pregled i uzimanje anamneze. Anamnestički podaci mogu ukazivati na skorašnju dijagnozu adneksalne mase, rekurentni abdominalni bol, i subfebrilnost. Kod dece starosti 2-14 godina sa visokom senzitivnošću i pozitivnom prediktivnom vrednošću može se primeniti Bolli score. Bolli score podrazumeva samo kliničke podatke pacijenta ali ne i imaging metode i identifikuje tri korisne kliničke varijabre na osnovu kojih je uspostavljen ovarian torsion score: godine starosti deteta, vreme trajanja bola i povraćanje. –Broj poena –broj godina, minus tri poena, ako je prisutno povraćanje, plus jedan poen ako je trajanje bola duže od 12 sati. Cut off vrednost Bolli-jevog scora kod devojčica je 11,5, niži skor označava veću verovatnoću da je u pitanju torzija jajnika [25,26].

LABORATORIJSKO ISPITIVANJE trebalo bi da uključi hematokrit, broj leukocita, humani horionski gonadotropin (HCG), elektrolite, i parametre inflamacije-C reaktivni protein (CRP) [2,22]. Laboratorijske analize mogu biti potpuno uredne, mogu ukazivati na anemiju kod rupture korpus luteuma ili leukocitozu i eleviran CRP-a usled nekroze tkiva i posledične inflamacije.

Nivo interleukina 6 je takođe povišen i ukazuje na povišeni oksidativni stres u torziji, ali je i nespecifični znak inflamacije i ne radi se rutinski u našoj kliničkoj praksi [27,28]. Određivanje tumor markera nije se pokazalo dovoljno senzitivnim ni specifičnim, mada elevacija određenih tumor markera može ukazati na samu prirodu torkvirane adneksalne mase. Fizikalni pregled usresređen je na palpaciju abdomena u cilju opipavanja tumorske mase i procene postojanja peritonealnog nadražaja. Najznačajnije su imidžing studije. Ultrazvuk je prva linija u postavljanju dijagnoze [29,30].

U pedijatrijskoj populaciji transabdominalni ultrazvučni pregled sa punom mokraćnom bešikom je inicijalna imaging metoda za evaluaciju torzije. Senzitivnost transabdominalnog ultrazvuka u pedijatrijskoj populaciji je 92-93% sa specifičnošću od 96-100%. U odraslih žena transvaginallni ultrazvuk pokazuje odličnu specifičnost, ali različitu senzitivnost,koja se kreće od 35-85% [31]. Ono sto se prati ultrazvučno je ovarijalni volumen, postojanje edema, postojanje adneksalne mase, prisustvo slobodne tečnosti i color doppler krvnih sudova jajnika odnosno tumorske mase. Postojanje razlike u volumenu jajnika uz dislokaciju istog je patognomoničan znak za ovarijalnu torziju. Drugi znak je postojanje edema normalnog ovarijalnog tkiva. U literaturi je opisan kao postojanje perifernih folikula sa hiperehogenim haloima u jajniku bez cističnih promena ili tumora- strings of pearls. Postojanje ovarijalnog edema ne treba biti pomešano sa postojanjem solidnog ovarijalnog tumora.

Torkvirani jajnik može biti okrugliji i uvećan u odnosu na kontralateralni, zbog otoka vaskularnih i limfnih sudova.Postoji normalan, redukovan ili potpuno odsutan protok kroz krvne sudove torkviranog jajnika [31-34]. Whirlpool sign je visoko senzitivan i specifičan znak za dijagnozu ovarijalne torzije. Whirlpool znak ukazuje na uvrnutu vaskularnu peteljku a dopler sonogram otkriva cirkularne krvne sudove unutar mase [32]. Na kraju, slobodna tečnost u manjoj količini može biti prisutna u Douglasovom špagu [31]. Najveći dijagnostički problem predstavljaju torzije bez torkvacije ipsilateralnog jajnika. Pokazano je da su u 31% svih torzija u pitanju inkompletne adneksalne torzije. Koristan znak torzije samo tube ali ne i jajnika je prisustvo tri ili više cisti u jednom redu [35]. Kombinacija prisustva slobodne tečnosti u maloj karlici, uvećanog jajnika i vaskularne abnormalnosti povećavaju senzitivnost i specifičnost ultrazvučnog nalaza. CT abdomenai malekarlice pokazuje visoku senzitivnost i specifičnost u evaluaciji suspektne torzije [36] i može ukazati na uvećan jajnik, njegovu dislokaciju i privlačenje uterusa na tu stranu, zadebljanje cistične mase, ascites, zadebljale zidove tube [36,37]. Definitivna dijagnoza postavlja se u operacionoj sali direktnom vizuelizacijom preparata.

feeding difficulties, abdominal distension, vomiting, and irritability. Ovarian torsion without infectious pathology may also be accompanied by low-grade fever. The low-grade fever is explained by necrotic changes in the torted ovary and occurs in 2–20% of patients. Physical examination may reveal low-grade fever, abdominal tenderness, abdominal pain, and a pelvic adnexal mass. A further diagnostic challenge is that 30% of patients—especially those in the premenarchal period—may have neither abdominal pain nor abdominal tenderness. [17,18,21-24].

**Diagnosis**

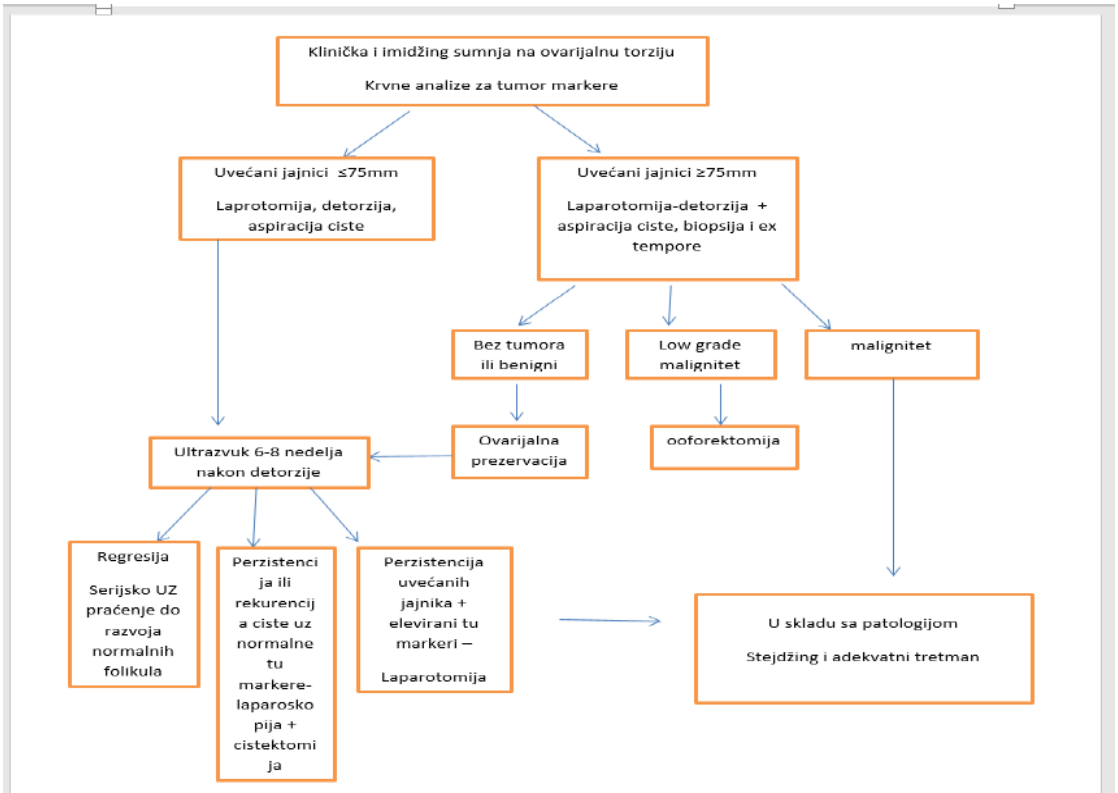
The diagnosis of ovarian torsion most often requires a combination of anamnestic data, clinical examination, and imaging methods. The first approach to the patient is the physical examination and taking the medical history. Anamnestic data may indicate a recent diagnosis of an adnexal mass, recurrent abdominal pain, and low-grade fever. In children aged 2–14 years, with high sensitivity and positive predictive value, the Bolli score can be applied. The Bolli score includes only the patient's clinical data but not imaging methods and identifies three useful clinical variables on the basis of which the ovarian torsion score is established: the age of the child, the duration of pain, and vomiting. –Number of points – number of years, minus three points if vomiting is present, plus one point if the duration of pain is longer than 12 hours. The cut-off value of the Bolli score in girls is 11.5, a lower score indicating a higher probability that ovarian torsion is present. [25,26].

LABORATORY TESTING should include hematocrit, leukocyte count, human chorionic gonadotropin (HCG), electrolytes, and inflammation parameters—C-reactive protein (CRP) [2,22]. Laboratory analyses may be completely normal, may indicate anemia in the case of corpus luteum rupture, or leukocytosis and elevated CRP due to tissue necrosis and consequent inflammation. The level of interleukin 6 is also elevated and indicates increased oxidative stress in torsion, but it is also a nonspecific sign of inflammation and is not routinely performed in our clinical practice [27,28]. Determining tumor markers has not proven to be sufficiently sensitive or specific, although the elevation of certain tumor markers may indicate the nature of the torted adnexal mass. The physical exam is focused on abdominal palpation in order to detect a tumor mass and assess the presence of peritoneal irritation. Imaging studies are the most important. Ultrasound is the first-line diagnostic tool [29,30].

In the pediatric population, transabdominal ultrasound with a full bladder is the initial imaging method for evaluating torsion. The sensitivity of transabdominal ultrasound in the pediatric population is 92–93%, with a specificity of 96–100%. In adult women, transvaginal ultrasound shows excellent specificity but variable sensitivity, ranging from 35–85% [31]. What is monitored on ultrasound is ovarian volume, presence of edema, presence of an adnexal mass, presence of free fluid, and color Doppler of ovarian or tumor mass blood vessels. The presence of a difference in ovarian volume with its displacement is a pathognomonic sign of ovarian torsion. Another sign is the presence of edema of normal ovarian tissue. In the literature, it is described as the presence of peripheral follicles with hyperechogenic halos in the ovary without cystic changes or tumors — strings of pearls. The presence of ovarian edema should not be mistaken for the presence of a solid ovarian tumor.

The torted ovary may be rounder and enlarged compared to the contralateral one due to swelling of vascular and lymphatic vessels. There may be normal, reduced, or completely absent blood flow through the vessels of the torted ovary [31–34]. The whirlpool sign is a highly sensitive and specific sign for the diagnosis of ovarian torsion. The whirlpool sign indicates the twisted vascular pedicle, and Doppler sonography reveals circular blood vessels within the mass [32]. Finally, a small amount of free fluid may be present in the pouch of Douglas [31]. The greatest diagnostic challenge is torsion without twisting of the ipsilateral ovary. It has been shown that 31% of all torsions are incomplete adnexal torsions. A useful sign of torsion involving only the tube but not the ovary is the presence of three or more cysts in one row [35]. The combination of free fluid in the pelvis, an enlarged ovary, and vascular abnormalities increases the sensitivity and specificity of ultrasound findings. CT of the abdomen and pelvis shows high sensitivity and specificity in the evaluation of suspected torsion [36] and may show an enlarged ovary, its displacement and pulling of the uterus to that

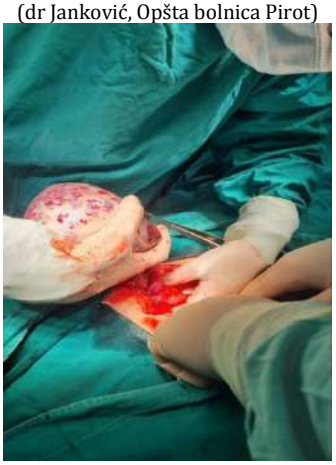
**Algoritam 1.** Algoritam za postupak kod kliničke i imidžing sumnje na postojanje ovarijalne torzije.




## Tretman i procena vijabilnosti jajnika

Tretman podrazumeva operativno lečenje i ujedno i konfirmaciju dijagnoze. Rana dijagnoza i hirurška terapija su neophodne kako bi zaštitile ovarijalnu i tubarnu funkciju i prevenirale ozbiljniji morbiditet. Minimiziranje ukupnog vremena u kome je jajnik u ishemiji je ključna komponenta u terapiji, ali vreme koje je potrebno da do ovarijalne nekroze dođe je nejasno [37,38].

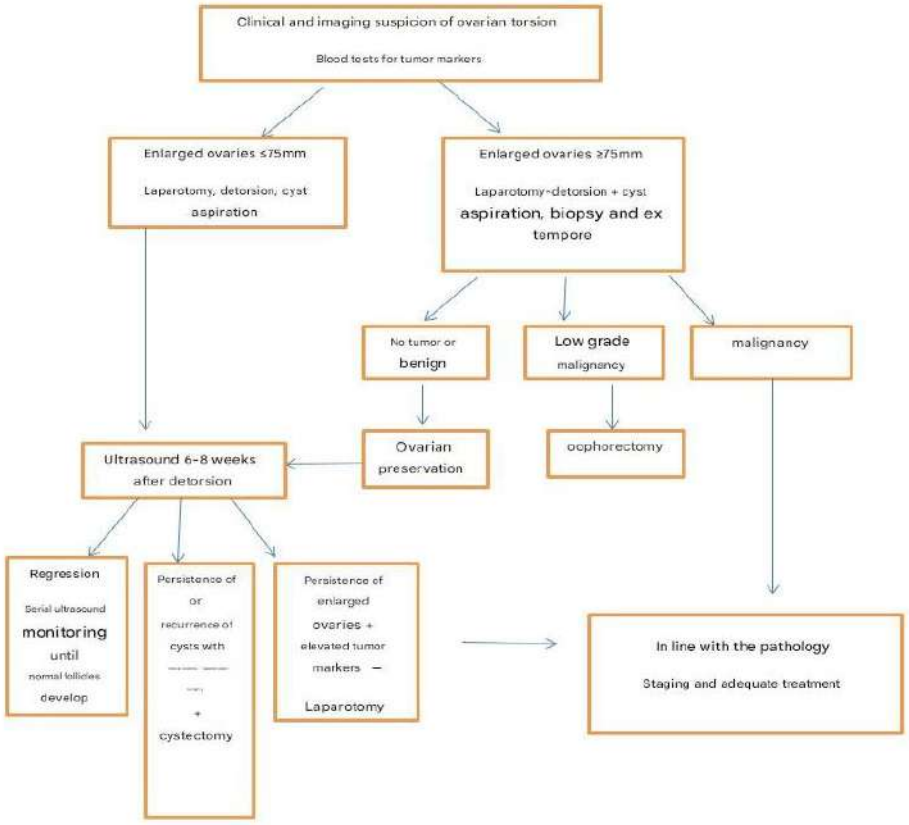
**Slika 1**. Operacija torkviranog fibrotekoma jajnika
(dr Janković, Opšta bolnica Pirot)



Sve dok su okludirani venski i limfni krvni sudovi pacijent može imati simptome neko vreme pre nego što se okludiraju i arterijski krvni sudovi [30,40,41]. U retrospektivnoj studiji kod pedijatrijske populacije, srednje vreme da se sačuva jajnik pre detorzije je 10,8h. Ako se detorzija izvrši u prvih 8h jajnik se sačuva u 40 % slučajeva, a u prvih 24h u 33% [42]. Ovaj nalaz je konzistentan sa podatkom da je kod žena procenat sačuvanih jajnika 30% ako se operacija uradi u prvih 24h od početka simptoma [43,44]. Različite studije pokazuju različito vreme od nastanka simptoma do detorzije u cilju očuvanja jajnika. Animalne studije su pokazale da se nekroza može desiti 36 sati od okluzije ili duže. Pedijatrijska i adultna

side, thickening of the cystic mass, ascites, thickened walls of the tube [36,37]. The definitive diagnosis is made in the operating room by direct visualization of the specimen..

**Algorithm 1.** Algorithm for management in cases of clinical and imaging suspicion of ovarian torsion.




**Treatment and assessment of ovarian viability**

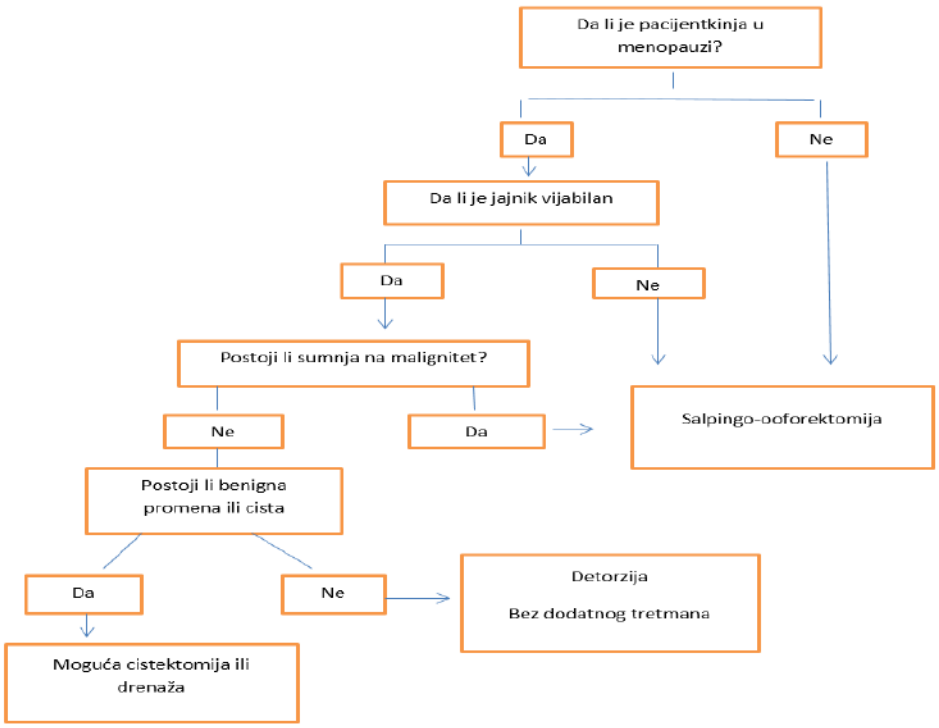
Treatment involves surgical management and at the same time confirmation of the diagnosis. Early diagnosis and surgical therapy are necessary in order to protect ovarian and tubal function and to prevent more serious morbidity. Minimizing the total time during which the ovary is in ischemia is a key component of therapy, but the time required for ovarian necrosis to occur is unclear. [37,38].

**Picture 1**. Surgery of a torted ovarian fibroma (Dr. Janković, General Hospital Pirot))

As long as the venous and lymphatic vessels are occluded, the patient may have symptoms for some time before the arterial vessels become occluded [30,40,41]. In a retrospective study of the pediatric population, the median time to save the ovary before

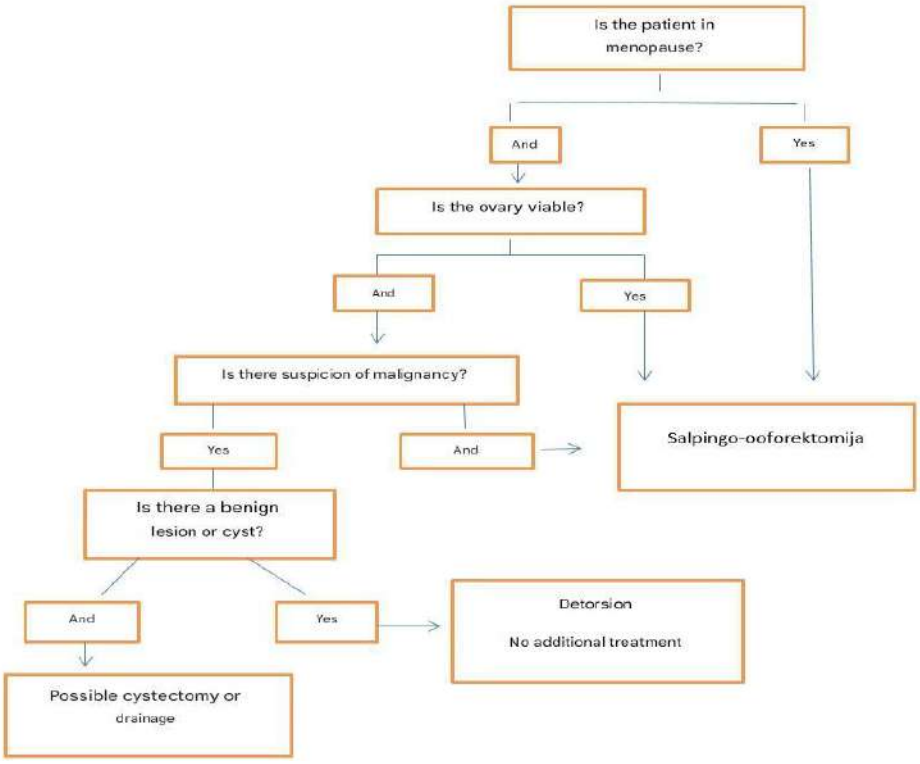
populacija pokazuju dobar dugoročni ishod kod detorzije bilo hemoragičnog bilo ishemijskog jajnika, sa normalnom produkcijom folikula kasnije u toku života u 90-94% opisanih [45,46]. Postoje dva metoda hirurškog lečenja - laparoskopski i laparotomija. Laparoskopija predstavlja razumnu alternativu. Benefit laparoskopije uključuje manju potrebu za analgeticima, ranu mobilizaciju, ima kozmetičku prednost, ranije otpuštanje iz bolnice na kućno lečenje. Dodatna pogodnost je što laparoskopska ovarijalna cistektomija je povezana sa manjom učestalošću formiranja adhezija nakon operacije u poređenju sa laparotomijom [47]. Laparotomija se preporučuje kada je suspektan maligni proces. Ono sto jeste neophodno to je procena ovarijalne vijabilnosti i očuvanje njegove funkcije. Jedini način da seproceni vijabilnost tog jajnika je gruba vizuelna inspekcija. Konvencionalno tamni i uvećani jajnik može biti samo u venskoj ili limfatičnoj kongestiji i može delovati nevijabilno, ali da postoji solidna verovatnoća da se radi o vijabilnom jajniku koji može povratiti svoju funkciju nakon detorzije [46]. Postoje i druge metode za procenu vijabilnosti jajnika poput ubrizgavanja fluoresceina i posmatranje protoka pod ultraljubičastom lampom [48]. Drugi način je ovarijalni bivalving, odnosno, laparoskopski se načini incizija jajnika električnom kukom - L hook, nakon detorzije, i posmatra se da li na načinjenom preseku ima krvotoka ili ne. To je ujedno i terapijski princip jer se smanjuje pritisak postignut venskom i limfatičnom kongestijom [49]. Ne postoji tačno utvrđeno vreme za koje može doći do nekroze jajnika. Siguran znak ovarijalne nekroze je želatinozna formacija koja se raspada prilikom manipulacije. Šta se očekuje od hirurškog lečenja? U najboljem slučaju detorzija [50], detorzija sa ovariopeksijom, ovarijalna cistektomija (preporučuje se kod benignih cista nakon detorzije) salpingoooforektomija kod suspektnih maligniteta, nekrotičnih jajnika i postmenopauzalnih žena.

**Algoritam 2.** Postupak kod žena u menopauzi



detorsion was 10.8 hours. If detorsion is performed within the first 8 hours, the ovary is preserved in 40% of cases, and within the first 24 hours in 33% [42]. This finding is consistent with data showing that in women, the percentage of preserved ovaries is 30% if surgery is performed within the first 24 hours from the onset of symptoms [43,44]. Different studies show varying times from symptom onset to detorsion in order to preserve the ovary. Animal studies have shown that necrosis can occur 36 hours or more after occlusion. Pediatric and adult populations show good long-term outcomes after detorsion of either hemorrhagic or ischemic ovaries, with normal follicle production later in life in 90–94% of cases described [45,46]. There are two surgical treatment methods — laparoscopy and laparotomy. Laparoscopy represents a reasonable alternative. The benefits of laparoscopy include reduced need for analgesics, early mobilization, cosmetic advantage, and earlier discharge to home care. An additional advantage is that laparoscopic ovarian cystectomy is associated with a lower incidence of postoperative adhesions compared to laparotomy [47]. Laparotomy is recommended when a malignant process is suspected. What is essential is the assessment of ovarian viability and preservation of its function. The only way to assess the viability of the ovary is by gross visual inspection. Conventionally, a dark and enlarged ovary may be only in venous or lymphatic congestion and may appear nonviable, but there is a substantial probability that it is a viable ovary that can regain function after detorsion [46]. There are other methods to assess ovarian viability, such as injecting fluorescein and observing the flow under ultraviolet light [48]. Another method is ovarian bivalving, i.e., laparoscopically making an incision in the ovary with an electric hook (L-hook) after detorsion and observing whether there is blood flow at the cut surface. This also serves a therapeutic purpose by reducing pressure caused by venous and lymphatic congestion [49]. There is no precisely determined time for ovarian necrosis to occur. A definitive sign of ovarian necrosis is a gelatinous formation that disintegrates upon manipulation. What is expected from surgical treatment? Ideally, detorsion [50], detorsion with oophoropexy, ovarian cystectomy (recommended for benign cysts after detorsion), or salpingo-oophorectomy in cases of suspected malignancy, necrotic ovaries, and postmenopausal women.

**Algorithm 2.** Procedure in menopausal women



**ZAKLJUČCI:**

- Ovarijalna torzija uglavnom zahvata žene u reproduktivnom periodu, ali signifikantan procenat nastaje i u premenarhalnom periodu, trudnica i postmenopauzalnih žena.
- Ovarijalna torzija nastaje kompletnom ili parcijalnom rotacijom jajnika i jajovoda koji dovodi do opstrukcije vaskularnog protoka.
- Krucijalni faktori za ovarijalnu torziju uključuju prisustvo ovarijalne mase kod žena u repoduktivnom periodu
- Skoro do 90% žena oseća abdominalnu bol koja počinje iznenada i oštrog je i intermitentnog karaktera.
- Do 70% oseća mučninu i ima povraćanje.
- Skoro 1/3 pacijenata sa torzijom nema abdominalni ili pelvičnu bol pri pregledu
- Iako se ultrazvuk koristi kao primarni dijagnostički modalitet u evaluaciji ovarijalne torzije sa visokom specifičnošću, normalni ultrazvučni nalaz ne može efektivno isključiti dijagnozu.
- CT abdomena i male karlice sa IV kontrastom može biti od pomoći pri dijagnozi.
- U evaluaciji za redukovano ili odsutno ovarijalno uvećanje, periferno pomeranje folikula, uvećani jajnici sa folikularnom stromom, i zadebljana tuba izgleda mete.

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**CONCLUSIONS:**

- Ovarian torsion mainly affects women of reproductive age, but a significant percentage also occurs in the premenarcheal period, in pregnant women, and in postmenopausal women.
- • Ovarian torsion occurs due to complete or partial rotation of the ovary and fallopian tube, leading to obstruction of vascular flow.
- • Crucial factors for ovarian torsion include the presence of an ovarian mass in women of reproductive age.
- • Almost 90% of women experience abdominal pain that begins suddenly, is sharp, and intermittent in nature.
- • Up to 70% experience nausea and vomiting.
- • Nearly one-third of patients with torsion have no abdominal or pelvic pain on examination.
- • Although ultrasound is used as the primary diagnostic modality in the evaluation of ovarian torsion with high specificity, a normal ultrasound finding cannot effectively rule out the diagnosis.
- • CT of the abdomen and pelvis with IV contrast can be helpful in diagnosis.
- • In the evaluation, findings for reduced or absent ovarian enlargement, peripheral displacement of follicles, enlarged ovaries with follicular stroma, and thickened fallopian tube are considered significant..

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# MALIGNI PLEURALNI MEZOTELIOM - PRIKAZ SLUČAJA

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ZDRAVSTVENI CENTAR KNJAŽEVAC

**Sažetak: Uvod.** Maligni pleuralni mezoteliom (MPM) je redak i vrlo agresivan tumor. Njegova pojava je uzročno povezana sa ekspozicijom azbestu kao vodećem etiološkom faktoru koji doprinosi nastanku bolesti u više od 80% slučajeva. Javlja se nakon inhalacije mikroskopskih azbestnih mineralnih vlakana, posle dugog latentnog perioda. Vreme koje protekne od ekspozicije azbestu do pojave tumora je nekoliko decenija. Veću učestalost ima kod muškaraca. Terapijski pristup se zasniva na multimodalnom principu, kombinaciji hirurgije, hemioterapije i radioterapije. Bez obzira na primenjenu terapiju, prognoza je uvek jako loša. **Cilj** rada je prikaz osnovnih karakteristika MPM i povećanja bazičnog znanja o štetnosti azbesta u nastanku bolesti. **Prikaz bolesnika:** Opisan je slučaj malignog mezotelioma pleure kod pacijenta muškog pola starosti 64 godine. Glavne tegobe su otežano disanje, kašalj, zamor na manji napor. Fizikalni nalaz nad plućima levo nečujandisajni šum. Inicijalna radiografija grudnog koša ukazuje na prisustvo masivnog pleuralnog izliva levo. Nakon načinjene drenaže levog pleuralnog prostora evakuisano 3000 ml tečnog sadržaja. Kasnije obavljena video asistirana torakoskopija (VATS), parcijalna dekortikacija pleure i biopsija gde jedijagnostifikovan MPM, epiteloidna varijanta. Najverovatniji kontakt sa azbestom se desio 30 do 35 godina ranije. **Zaključak:** Opisan slučaj MPM prikazuje pacijenta koji je imao tipične nespecifične simptome na početku, karakterističan jednostrani pleuralni izliv,a kasnije bolove jakog intenziteta u predelu grudnog koša i brzu progresiju bolesti.Bolest se najčešće otkriva u odmaklom stadijumu. Anamnestički podaci o mogućem kontaktu sa azbestom u toku života mogu pobuditi sumnju, doprineti nešto ranijoj dijagnozi, kada su terapijske mogućnosti nešto veće.
**Ključne reči:** muški pol, maligni mezoteliom, mineralna vlakna, pleura, azbest, prognoza.

## UVOD

Maligni mezoteliom je relativno redak, ali vrlo agresivan tumor. Predstavlja multifaktorijalno oboljenje u čijem nastanku ulogu imaju: azbest, Simijan virus 40 i radioterapija [1]. Nije dokazano da pušenje uzrokuje pojavu MPM, ali doprinosi njegovom nastanku. Prema podacima iz literature njegova pojava je uzročno povezana sa ekspozicijom azbestu kao vodećem etiološkom faktoru koji doprinosi nastanku bolesti u više od 80% slučajeva. Javlja se nakon inhalacije mikroskopskih azbestnih mineralnih vlakana suspendovanih u vazduhu, posle dugog latentnog perioda od nekoliko decenija. Daleko veću učestalost ima kod muškaraca, što se objašnjava činjenicom da se muškarci češće bave zanimanjima koja su „rizična" u smislu kontakta sa azbestom. Profesionalna ekspozicija azbestu bila je predmet brojnih studija.Ovakva povezanost MPM sa profesijom je najverovatnije posledica nesprovođenja mera zaštite na radu.Posebno je zabrinjavajuća činjenica da dolazi do pojave mezotelioma kod članova porodice ovih radnika.Bolest se češće javlja i u mestima gde se nalaze rudnici ove materije, jer usled eksploatacije dolazi do kontaminacije životne sredine (vazduha) i izlaganja stanovništva azbestu (endemska područja) [2]. Kao karcinogeni materijal, azbest je zabranjen u svim zemljama članicama Evropske unije 2005. godine, dok jeSrbija 2011. godine donela zabranu korišćenja azbesta u svim proizvodima, a propisan je i Pravilnik o postupanju sa otpadom koji sadrži azbest [3].

## PRIKAZ SLUČAJA

Pacijent muškog pola starosti 64 godine. Mašin-bravar u penziji. Pušač, preko 40 godina, po 20 cigareta dnevno, retko konzumira alkohol. U ličnoj anamnezi prethodno zdrav, bez drugih komorbiditeta. Pacijent navodi da je prve tegobe osetio početkom juna 2018. god. Glavne tegobe su otežano disanje, osećaj gušenja i zamor na manji napor. Kašalj je prisutan nekoliko meseci pre toga, od marta 2018. Povišen krvni pritisak


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# MALIGNANT PLEURAL MESOTHELIOMA – CASE REPORT

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HEALTH CENTER KNJAŽEVAC

**Summary: Introduction.** Malignant pleural mesothelioma (MPM) is a rare and highly aggressive tumor. Its occurrence is causally linked to asbestos exposure, which is the leading etiological factor contributing to the development of the disease in more than 80% of cases. It occurs after inhalation of microscopic asbestos mineral fibers, following a long latent period. The time from asbestos exposure to tumor onset is usually several decades. The disease is more common in men. The therapeutic approach is based on a multimodal strategy, combining surgery, chemotherapy, and radiotherapy. Regardless of the treatment applied, the prognosis is always very poor. The aim of this paper is to present the basic characteristics of MPM and to increase fundamental knowledge about the harmful effects of asbestos in the development of the disease. **Case presentation:** A case of malignant pleural mesothelioma in a 64-year-old male patient is described. The main symptoms included dyspnea, cough, and fatigue on minimal exertion. Physical examination of the lungs revealed absent breath sounds on the left side. The initial chest X-ray indicated the presence of a massive left-sided pleural effusion. After drainage of the left pleural space, 3000 ml of fluid was evacuated. A video-assisted thoracoscopic surgery (VATS) was subsequently performed, along with partial pleural decortication and biopsy, which confirmed the diagnosis of MPM, epithelioid subtype. The most likely asbestos exposure occurred 30 to 35 years earlier. **Conclusion**: The presented case of MPM describes a patient who initially exhibited typical nonspecific symptoms, a characteristic unilateral pleural effusion, and later severe chest pain with rapid disease progression. The disease is most often diagnosed at an advanced stage. A history suggesting possible asbestos exposure during the patient's lifetime may raise suspicion and contribute to an earlier diagnosis, at a stage when therapeutic options are somewhat greater..

**Ključne reči:** male sex, malignant mesothelioma, mineral fibers, pleura, asbestos, prognosis.

## INTRODUCTION

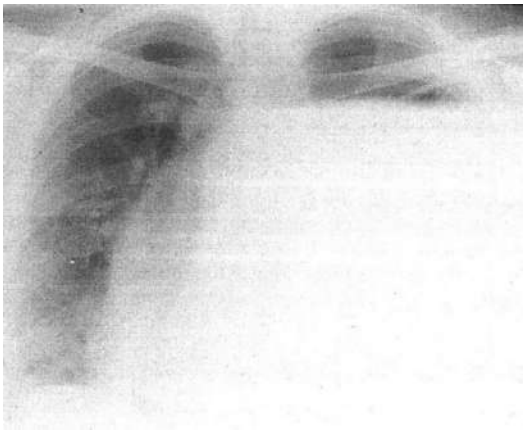
Malignant mesothelioma is a relatively rare but very aggressive tumor. It represents a multifactorial disease in whose development the following factors play a role: asbestos, Simian virus 40, and radiotherapy [1]. It has not been proven that smoking causes the occurrence of MPM, but it contributes to its development. According to data from the literature, its occurrence is causally related to asbestos exposure as the leading etiological factor that contributes to the development of the disease in more than 80% of cases. It appears after inhalation of microscopic asbestos mineral fibers suspended in the air, after a long latent period of several decades. It has a much higher incidence in men, which is explained by the fact that men are more often engaged in occupations that are "risky" in terms of asbestos exposure. Occupational exposure to asbestos has been the subject of numerous studies. Such an association of MPM with occupation is most likely the consequence of not implementing occupational safety measures. A particularly concerning fact is the occurrence of mesothelioma in family members of these workers. The disease also more frequently appears in places where mines of this material are located, because exploitation leads to contamination of the environment (air) and exposure of the population to asbestos (endemic areas) [2]. As a carcinogenic material, asbestos was banned in all European Union member states in 2005, while Serbia introduced a ban on the use of asbestos in all products in 2011, and a Regulation on handling waste containing asbestos was also prescribed. [3].

## CASE REPORT

The patient is a 64-year-old male. A retired machine locksmith. Smoker for over 40 years, about 20 cigarettes per day, rarely consumes alcohol. In his personal medical history previously healthy, without other comorbidities. The patient states that he felt the

dve nedelje unazad TA 160/100 mmHg, pre toga normalan krvni pritisak. Sagledan od strane interniste, dobio antihipertenzivnu terapiju i dalje upućen pneumofiziologu. Auskultatorno nad plućima levo potpunonečujno disanje, bez propratnih zvukova, a nalaz nad ostalim delovima pluća je normalan disajni šum. Saturacija kiseonika u krvi je 97%.

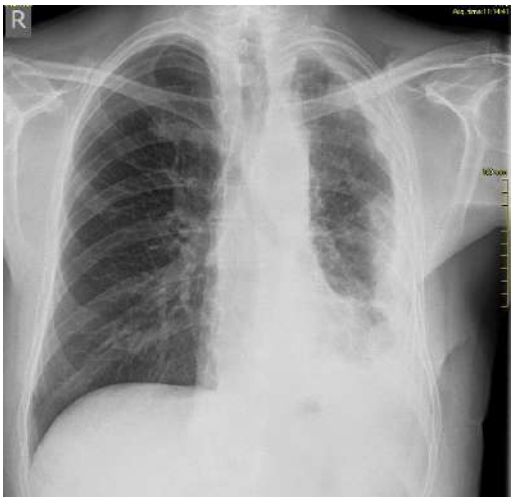
**Slika 1.** Inicijalna radiografija grudnog koša



Radiografija grudnog koša (Slika1) ukazuje na hidropneumotoraks levo, sa infraklavikularno prisutnim hidroaeričnim nivoom. Srčana senka potisnuta put desno. Sve laboratorijske i biohemijske analize su u referentnim vrednostima. Nakon obavljenih osnovnih laboratorijskih i dijagnostičkih pretraga u Zdravstvenom Centru Knjaževac, pacijent je dalje upućen SB za Plućne bolesti Ozren 26.06.2018. godine. Dalje biva preveden na Kliniku za grudnu hirurgiju UKC Niš dva dana kasnije, radi daljeg lečenja, gde je u narednom periodu u više navrata hospitalizovan. Pri prvoj hospitalizaciji na ovoj klinici inicijalno je načinjena drenaža levog pleuralnog prostora, pri tom evakuisano oko 3000 ml tečnog sadržaja. Citološka i bakteriološka analize nisu ukazivale na prisustvo tumorskih ćelija, kao ni infekcije.

Prilikom sledeće hospitalizacije operisan je 24.07.2018. godine, urađena je videoasistirana torakoskopija (VATS), parcijalna dekortikacija pleure i biopsija, materijal poslat na patohistološki pregled. U patohistološkom nalazu od 11.09.2018. godine, dijagnostifikovan je maligni mezoteliom pleure, epiteloidna varijanta. Na kontrolnoj PA radiografiji grudnog koša od 16.09.2018. godine (Slika 2) Leva hemidijafragma i levi KF sinus zasenjeni senkom laterouzlaznog toka-prisutna pleuralna efuzija. Ostali deo plućnog parenhima levo smanjene transparencije.

**Slika 2.** Kontrolna radiografija grudnog koša

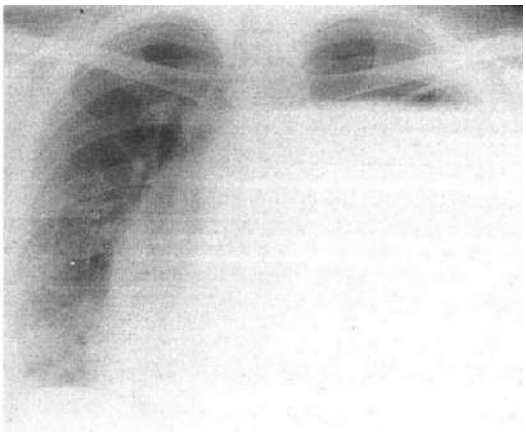



U zaključku MSCT pluća od 24.09.2018. godine: u pleuralnoj duplji, levo prisutna heterodenzna promena difuzno sa gušćim tečnim sadržajem, sa kompresivnom atelektazom i mekotkivnom komponentom, opisana promena u prvom redu odgovara neoplastičnoj promeni sa empijemom. U ostalom plućnom parenhimu su prisutne mikronodularne promene i medijastinalna limfadenomegalija. Na koštanim strukturama, osim degenerativnih, nema drugih MSCT promena.

Po odluci Konzilijuma za pulmološku onkologiju od 25.09.2018. godine planirano lečenje prvom linijom hemioterapije po režimu pemetreksedcisplatin. U međuvremenu dolazi do daljeg napredovanja bolesti. Prisutni su slab apetit i progresivni gubitak težine. Suspektna je pojava centralne simptomatologije u vidu otežane komunikativnosti, povremene dezorjentisanosti u vremenu, nestabilnosti, periodičnog gubitka kontrole sfinktera (povremeno umokravanje). Bolovi stalno prisutni. Od analgetske terapije primenjeni Ibuprofen tbl 600mg 2x1, Tramadol tbl 50mg 2-3x1, ali zbog nedovoljnog analgetskog efekta ubrzo zatim započeta upotreba Fentaniltransdermalnog flastera 25 mikrograma/h. Pacijent je hospitalizovan na Klinici za onkologiju UKC Niš 15.10.2018. godine. U laboratorijskim i biohemijskim

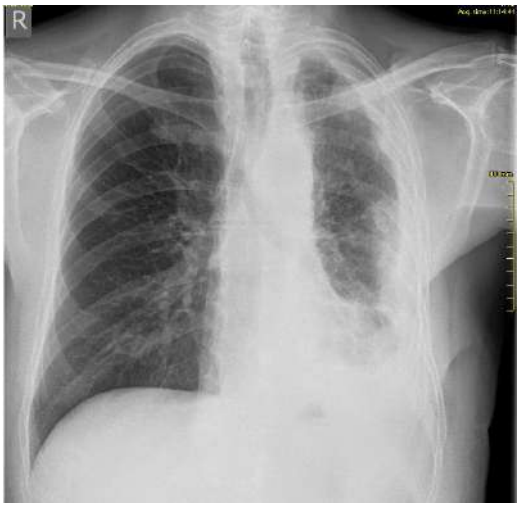
first symptoms at the beginning of June 2018. The main complaints are shortness of breath, a feeling of choking, and fatigue on minimal exertion. Cough has been present for several months before that, since March 2018. Elevated blood pressure for the past two weeks, BP 160/100 mmHg, previously normal blood pressure. Evaluated by an internist, received antihypertensive therapy and was further referred to a pneumophysiologist. Auscultation of the lungs on the left reveals completely absent breath sounds, without accompanying sounds, while in the other parts of the lungs the breath sounds are normal. Blood oxygen saturation is 97%.

**Figure 1.** Initial chest radiograph



Chest radiography (Figure 1) indicates a left hydropneumothorax, with an infraclavicularly present hydro-air level. The cardiac silhouette is displaced to the right. All laboratory and biochemical analyses are within reference values. After the basic laboratory and diagnostic examinations performed at the Health Center Knjaževac, the patient was further referred to the Special Hospital for Pulmonary Diseases Ozren on 26.06.2018. Two days later he was transferred to the Clinic for Thoracic Surgery, University Clinical Center Niš, for further treatment, where he was hospitalized several times in the following period. During the first hospitalization at this clinic, an initial drainage of the left pleural space was performed, with approximately 3000 ml of fluid evacuated. Cytological and bacteriological analyses did not indicate the presence of tumor cells or infection.
During the next hospitalization, surgery was performed on 24.07.2018., video-assisted thoracoscopy (VATS), partial pleural decortication and biopsy were done, and the material was sent for histopathological examination. In the histopathological report dated 11.09.2018., malignant pleural mesothelioma, epithelioid variant, was diagnosed. On the follow-up PA chest radiograph from 16.09.2018. (Figure 2), the left hemidiaphragm and left costophrenic angle are obscured by a laterally ascending shadow—pleural effusion is present. The remaining part of the lung parenchyma on the left shows reduced transparency.

**Figure 2.** Control radiography of the chest




In the conclusion of the chest MSCT dated 24.09.2018: in the pleural cavity on the left, a heterogeneous-density lesion is present diffusely, with denser fluid content, accompanied by compressive atelectasis and a soft-tissue component; the described lesion primarily corresponds to a neoplastic process with empyema. In the remaining lung parenchyma, micronodular changes and mediastinal lymphadenopathy are present. In the bony structures, apart from degenerative changes, there are no other MSCT findings.

According to the decision of the Pulmonology Oncology Council from 25.09.2018, treatment with first-line chemotherapy using the pemetrexed–cisplatin regimen was planned. In the meantime, further disease progression occurred. Poor appetite and progressive weight loss were present. The appearance of central neurological symptoms was suspected, including impaired

analizama registruju se azotemija i hiperkalcemija (urea 16,4 mmol/L, creat 179,4 umol/L, Ca 4,26 mmol/L). Zbog kliničkog pogoršanja, slabijeg performans statusa nije indikovana primena hemioterapije. Usled povišenih vrednosti serumskog kalcijuma donešena odluka o primeni bifosfonata i urgentno započeta terapija. Primenjena terapija Zolendronska kiselina amp 4mg protekla je uredno. Međutim, dolazi do produbljivanja centralne simptomatologije i pacijent egzitira pre prvog ciklusa planirane sistemske terapije.

Zbog specifične prirode i raznovrsnosti poslova kojim se bavio ekspozicija azbestu je verovatno bila prisutna u više navrata u toku života. Ali najverovatnije kritično izlaganje azbestu moglo je da se dogodi 30 do 35 godina ranije.

**DISKUSIJA**

Maligni mezoteliom može imati različitu lokalizaciju, nastaje od mezotelnih ćelija seroznih membrana koje oblažu telesne šupljine i organe (visceralna ili parijetalna pleura, peritoneum, perikard ili najređe ovojnica drugih organa npr tunike vaginalis testisa). Najčešće dijagnostifikovan je maligni mezoteliom pleureu preko 70% slučajeva. Tumor se javlja nakon veoma dugog latentnog perioda od nekoliko decenija. Vreme od ekspozicijie azbestu do pojave tumora je najmanje 25, a po nekim autorima i duže od 50 godina. Zbog dugog latentnog perioda MPM se najčešće dijagnostifikuje kod pacijenata starijih od 60 godina. Među bolesnicima kod kojih je potvrđeno postojanje rizičnog zanimanja, najčešće su bili mašin-bravari, kao i naš pacijent [1,4].

Azbest obuhvata šest prirodnih silikatnih minerala. Sačinjen je od mekanih, tankih, svilenkastih vlaknastih kristala. Postoje dva tipa azbestnih vlakana: amfibolni (najčešće korišćen krocidolit ili plavi; amozit ili smeđi azbest; čija su vlakna duža, tanka i prava-nalik na iglice) i serpentinski (krizotil ili beli azbest; čija vlakna imaju serpentinski oblik) [5]. Azbest je bio u širokoj upotrebi u celom svetu, posebno u drugoj polovini prošlog veka. Zbog svojih povoljnih fizičkih osobina imao je široku primenu: dobar je provodnik toplote, ne gori i ne ugljeniše se i dugotrajan je. Sve forme azbestnih vlakana mogu biti odgovorna za pojavu oboljenja. Neke forme azbestnih vlakana su patogenija od drugih. Vlakna koja su tanja i duža imaju najveći karcinogeni potencijal. Sve vrste azbesta su veoma stabilne, tokom vremena ne podležu degradaciji spontano, međutim, njegovom obradom ili oštećenjem stvara se azbestna prašina. Ova prašina se lako inhalira i dolazi do alvelernih sakulusa. Nije dovoljno razjašnjeno kojim putem azbestna vlakna dospevaju do pleure i mezotelnih ćelija. Ali u dugom vremenskom periodu ova vlakna dovode do hronične inflamacije, fibroziranja i maligne alteracije. Onkogeneza nije dovoljno poznata. MPM najverovatnije nastaje kao rezultat inaktivacije tumor supresornih gena. Najčešći je gubitak funkcije tumor supresornog gena CDKN2A, inaktivacija NF2 i mutacija ili delecija BAP-1 tumor supresornog gena (protein-1 povezan sa BRCA1) [6]. Svi ovi faktori zajedno utiču na nastanak MPM.

Simptomi mezotelioma variraju u zavisnosti od lokalizacije i stadijuma bolesti. Nakon dugog latentnog perioda početni simptomi su najčešće nespecifični i blagi. Kod mezotelioma pleure prisutne su tegobe sa disanjem, progresivna dispneja, i brzo zamaranje i na najmanji napor. U ovom prikazu, kod našeg pacijenta, svi navedeni simptomi su bili prisutni. Kašalj je suv i umara bolesnika, a može da dođe do pojave iskašljavanja krvi. Naš pacijent nije imao pojavu iskašljavanja krvi (hemoptizije), ali je kašalj bio prisutan. Neki od simptoma mogu biti posledica pleuralne efuzije. Povišen krvni pritisak nije opisan kao simptom MPM, ali je kod našeg pacijenta verovatno posledica masivnog levostranog pleuralnog izliva. Pleuralni izlivi mogu biti masivni i često su rekurentni. U fazi povlačenja izliva dolazi do prolaznog olakšanja, a zatim se javlja bol. Bol u grudnom košu je vodeći simptom MPM. Smatra se da se javlja zbog urastanja tumora u okolne strukture. Bol u grudnom košu jakog intenziteta bio je prisutan i kod pacijenta u našem prikazu. Neurološki simptomi kod prikazanog pacijenta su moguća posledica diseminacije bolesti u CNS.

Neke od opštih simptoma kao što su malaksalost, opšta slabost, umor, gubitak apetita, gubitak težine imao je i naš pacijent tokom kasnijeg razvoja bolesti. Nekada se javljaju temperatura, groznica, noćno preznojavanje. Uglavnom su to simptomi uznapredovale bolesti.

Standardna radiografija grudnog koša je dijagnostička metoda prve linije, iako nije dovoljno senzitivna i specifična. Čest nalaz na radiografiji je prisustvo jednostranog pleuralnog izliva. Citološka analiza punktiranog pleuralnog

communication, occasional disorientation to time, instability, and intermittent loss of sphincter control (occasional urinary incontinence). Pain was constantly present. From analgesic therapy, Ibuprofen 600 mg tablets 2×1 and Tramadol 50 mg tablets 2–3×1 were administered, but due to insufficient analgesic effect, the use of a Fentanyl transdermal patch 25 micrograms/h was soon initiated. The patient was hospitalized at the Oncology Clinic, University Clinical Center Niš, on 15.10.2018. Laboratory and biochemical analyses showed azotemia and hypercalcemia (urea 16.4 mmol/L, creatinine 179.4 μmol/L, Ca 4.26 mmol/L). Due to clinical deterioration and poorer performance status, chemotherapy was not indicated. Because of the elevated serum calcium levels, a decision was made to administer bisphosphonates, and urgent treatment was initiated. Therapy with Zoledronic acid 4 mg ampoule was administered without complications. However, progressive central neurological deterioration ensued, and the patient died before the first cycle of the planned systemic therapy.

Due to the specific nature and diversity of his occupations, asbestos exposure was likely present on multiple occasions throughout his life. However, the most probable critical exposure to asbestos may have occurred 30 to 35 years earlier..

## DISCUSSION

Malignant mesothelioma can have different localizations and arises from mesothelial cells of serous membranes that line body cavities and organs (visceral or parietal pleura, peritoneum, pericardium, or, rarely, the coverings of other organs, e.g., the tunica vaginalis of the testis). Most commonly diagnosed is malignant pleural mesothelioma (MPM), accounting for over 70% of cases. The tumor appears after a very long latent period of several decades. The time from asbestos exposure to tumor development is at least 25 years, and according to some authors, more than 50 years. Due to this long latent period, MPM is most often diagnosed in patients over 60 years of age. Among patients with confirmed high-risk occupations, the most common were machine-fitters, as in our patient [1,4].

Asbestos includes six naturally occurring silicate minerals. It consists of soft, thin, silky fibrous crystals. There are two types of asbestos fibers: amphibole (most commonly used: crocidolite or blue; amosite or brown asbestos; fibers are long, thin, and straight – needle-like) and serpentine (chrysotile or white asbestos; fibers have a serpentine shape) [5]. Asbestos was widely used worldwide, especially in the second half of the last century. Due to its favorable physical properties, it had broad applications: it is a good conductor of heat, does not burn or carbonize, and is durable. All forms of asbestos fibers can be responsible for disease development. Some forms are more pathogenic than others. Thinner and longer fibers have the greatest carcinogenic potential. All types of asbestos are very stable and do not degrade spontaneously over time; however, processing or damage produces asbestos dust. This dust is easily inhaled and reaches the alveolar sacs. The exact mechanism by which asbestos fibers reach the pleura and mesothelial cells is not fully clarified. Over a long period, these fibers cause chronic inflammation, fibrosis, and malignant alterations. Oncogenesis is not fully understood. MPM most likely arises as a result of inactivation of tumor suppressor genes. The most frequent changes are loss of function of the CDKN2A tumor suppressor gene, NF2 inactivation, and mutation or deletion of the BAP-1 tumor suppressor gene (BRCA1-associated protein 1) [6]. All these factors together contribute to the development of MPM.

Symptoms of mesothelioma vary depending on the localization and stage of the disease. After a long latent period, initial symptoms are usually nonspecific and mild. In pleural mesothelioma, complaints include breathing difficulties, progressive dyspnea, and rapid fatigue with minimal exertion. In our patient, all these symptoms were present. The cough was dry and exhausting, and hemoptysis (coughing up blood) may occur. Our patient did not have hemoptysis, but the cough was present. Some symptoms may result from pleural effusion. Elevated blood pressure is not described as a symptom of MPM, but in our patient, it was likely a consequence of massive left-sided pleural effusion. Pleural effusions can be massive and often recurrent. During effusion drainage, transient relief occurs, followed by pain. Chest pain is the leading symptom of MPM and is thought to result from tumor infiltration into surrounding structures. Severe chest pain was also present in our patient. Neurological symptoms in the patient may be a possible consequence of disease dissemination to the CNS.

izliva ima senzitivnost od 13 do čak 75%, ali može biti negativna ili lažno negativna. U opisanog pacijenta je bila negativna. CT grudnog koša je nezaobilazna dijagnostička procedura, koja pruža dragocene podatke, o izgledu pleure (zadebljnje, kalcifikacije), karakteristikama izliva (ako je prisutan) i stanju medijastinalnih limfnih nodusa i organa.

Perkutana biopsija je terapijski i dijagnosticki postpupak MPM. Videoasistirana torakoskopija (VATS) je najpouzdanija metoda kojom se obezbeđuje adekvatan uzorak za morfološku i imunohistohemijsku analizu.

Makroskopski ovi tumori daju izgled difuznog pleuralnog zadebljanja. Patohistološka dijagnostika je zlatni standard. Histološki su podeljeni na subtipove: epiteloidni, sarkomatoidni i bifazični, koji je sastavljen iz mešavine ova dva tipa [1,4]. Kod našeg pacijenta postavljena je dijagnoza epiteloidnog tipa MPM, koji ima najveću učestalost od oko 60%. Bolje je prognoze, bolje reaguje na terapiju i ima duže prosečno preživljavanje. Iako postoje tri histološka subtipa MPM, SZO je 2021. godine dala složenu i sveobuhvatnu podelu Tumora pleure i perikardijuma [7,8]. Uzevši u obzir histološke karakteristike, prognozu, proširenost, osobine BAP1 tumor supresornog gena imunohistohemije, homozigotnu deleciju CDKN2A i drugo.

Terapijski pristup je zasnovan na multimodalnom pristupu, kombinacijom hirurgije, hemioterapije, radioterapije i imunoterapije. Iako je poslednjih godina postignut značajan napredak u lečenju, terapijske mogućnosti su ograničene. Trenutni terapijski modaliteti produžavaju preživljavanje, ali ne daju kompletno izlečenje.

Na operabilnost utiče veličina tumorske mase i opšte stanje bolesnika. Operabilni su stadijumi I do IIIa, kada je tumor još uvek lokalizovan, ukoliko se radi o epitelioidnom tipu MPM. U kasnijim stadijumima sa prisutnim metastazama hirurgija ima palijativnu korist.

Hemoterapija je najkorišćeniji modalitet lečenja mezotelioma, primenjuje se u svim stadijumima. Pemetreksed i cisplatin čine prvu liniju hemioterapije. Neki pacijenti mogu imati bolji odgovor na drugu preporučenu kombinaciju pemetreksed i karboplatin, ili kombinaciju cisplatin i gemcitabin [9].

Radioterapijase najčešće primenjivala palijativno za olakšanje simptoma kod pacijenata sa kasnijim stadijumima, ali tehnički napredak omogućio je korak napred u lečenju MPM [10].

Poslednjih godina primenjuje se imunoterapija monoklonskim antitelima. Nivolumab u kombinaciji sa ipilimumabom je indikovan kao prva linija za lečenje pacijenata sa neresektabilnim MPM. Lečenje traje do progresije bolesti, neprihvatljive toksičnosti ili do 24 meseca. Ovako lečeni pacijenti imali su značajno poboljšanje [11].

Maligni mezoteliom pleure je jako agresivan tumor. Bolest je neizlečiva u poznijim stadijumima. Prognoza bolesti je uvek jako loša. Očekivano vreme preživljavanja je manje od 18 meseci od pojave prvih simptoma, dok je vreme preživljavanja za uznapredovalu bolest, bez terapije 6-8 meseci.

Prema istraživanju sprovedenom 2019. godine u endemskom području Turske [2], rezultati postoperativnog preživljavanja pacijenata pokazali su da je srednji period preživljavanja bio 19,6 meseci. Na uzorku od 13 pacijenata, najduže preživljavanje od 32 meseca bio je kod pacijenta koji je nakon pleuralne dekortikacije podvrgnut postoperativnoj hipertermičnoj hemioterapiji.

## ZAKLJUČAK

Postoje podaci u anamnezi na koje treba obratiti pažnju: pol, godine (stariji od 60 godina, zbog dugog latentnog perioda), zanimanje, pušači. Opisan slučaj prikazuje tipičnog pacijenta sa MPM, koji je u početku imao tipične nespecifične simptome, u vidu kašlja, dispneje, zamaranja i karakterističan jednostrani pleuralni izliv, a kasnije bolove jakog intenziteta u predelu grudnog koša i brzu progresiju bolesti. Bolest se najčešće otkriva u odmaklom stadijumu. Anamnestički podaci o mogućem kontaktu sa azbestom u toku života mogu pobuditi sumnju, doprineti nešto ranijoj dijagnozi, kada su terapijske mogućnosti nešto veće, a koje mogu za izvesno vreme produžiti život obolelima. Najvažnija je primarna prevencija, sprečiti izlaganje azbestu ili na bezbedan način ukloniti azbestni materijal. MPM je retka bolest, ali treba misliti o njoj u diferencijalnoj dijagnozi, jer je ovo vrlo agresivan tumor.

Some general symptoms, such as malaise, general weakness, fatigue, loss of appetite, and weight loss, were also present in our patient during the later course of the disease. Occasionally, fever, chills, and night sweats may occur, usually in advanced stages of the disease.

Standard chest radiography is a first-line diagnostic method, although it is not sufficiently sensitive or specific. A common finding on radiography is the presence of a unilateral pleural effusion. Cytological analysis of punctured pleural fluid has a sensitivity ranging from 13% to 75%, but it may be negative or false-negative. In the described patient, it was negative. Chest CT is an indispensable diagnostic procedure that provides valuable information about the pleura (thickening, calcifications), characteristics of effusions (if present), and the condition of mediastinal lymph nodes and organs.

Percutaneous biopsy is both a diagnostic and therapeutic procedure for MPM. Video-assisted thoracoscopy (VATS) is the most reliable method, providing an adequate sample for morphological and immunohistochemical analysis. Macroscopically, these tumors appear as diffuse pleural thickening. Pathohistological diagnosis is the gold standard. Histologically, tumors are divided into subtypes: epithelioid, sarcomatoid, and biphasic, which consists of a mixture of the two types [1,4]. In our patient, the diagnosis of epithelioid MPM was established, which is the most frequent type, accounting for about 60% of cases. It has a better prognosis, responds better to therapy, and has longer average survival. Although there are three histological subtypes of MPM, the WHO in 2021 proposed a complex and comprehensive classification of pleural and pericardial tumors [7,8], taking into account histological characteristics, prognosis, disease extent, BAP1 tumor suppressor gene immunohistochemistry, CDKN2A homozygous deletion, and other factors.

The therapeutic approach is based on a multimodal strategy, combining surgery, chemotherapy, radiotherapy, and immunotherapy. Despite significant progress in recent years, treatment options remain limited. Current therapeutic modalities prolong survival but do not provide complete cure.

Operability depends on tumor size and the patient's general condition. Stages I to IIIa are operable if the tumor is still localized and of the epithelioid type. In later stages with metastases, surgery has a palliative benefit.

Chemotherapy is the most commonly used treatment modality for mesothelioma and is applied in all stages. Pemetrexed and cisplatin constitute the first-line chemotherapy regimen. Some patients may respond better to other recommended combinations, such as pemetrexed with carboplatin, or cisplatin with gemcitabine [9]. Radiotherapy has most often been applied palliatively to relieve symptoms in later stages of disease, although technical advances have allowed significant improvements in MPM management [10].

In recent years, immunotherapy with monoclonal antibodies has been implemented. Nivolumab in combination with ipilimumab is indicated as first-line treatment for patients with unresectable MPM. Treatment continues until disease progression, unacceptable toxicity, or for up to 24 months. Patients treated in this way have shown significant improvement [11].

Malignant pleural mesothelioma is a highly aggressive tumor. The disease is incurable in later stages, and the prognosis is always very poor. Expected survival is less than 18 months from the onset of initial symptoms, while survival for advanced disease without therapy is 6–8 months.

According to a study conducted in 2019 in an endemic area of Turkey [2], postoperative survival results showed a median survival period of 19.6 months. Among 13 patients, the longest survival of 32 months was observed in a patient who underwent postoperative hyperthermic chemotherapy after pleural decortication..

## CONCLUSION

There are anamnesis data that deserve attention: sex, age (over 60 years, due to the long latent period), occupation, and smoking history. The described case represents a typical patient with MPM, who initially presented with typical nonspecific symptoms such as cough, dyspnea, and fatigue, along with a characteristic unilateral pleural effusion, and later developed severe chest pain and rapid disease progression. The disease is most often diagnosed at an advanced stage. Anamnestic data regarding possible asbestos exposure during life may raise suspicion and contribute to an earlier diagnosis, at a stage when therapeutic options are

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somewhat greater and may, for a limited time, prolong survival. The most important measure is primary prevention: to prevent asbestos exposure or to safely remove asbestos-containing material. MPM is a rare disease, but it should be considered in the differential diagnosis, as it is a highly aggressive tumor..

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# LEČENJE OBOLELIH OD PARODONTITISA (PARODONTOPATIJA) KROZ ISTORIJU

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**Sažetak:** Sačuvani biološki ostaci zuba i vilica iz praistorije sa znacima oboljenja tkiva parodoncijuma, ukazuju da su ova oboljenja stara koliko i ljudski rod. Dokazi o interesovanju ljudi za oralno zdravlje su mnogobrojni i datiraju još iz perioda pre nove ere. Najstarije civilizacije i njihovo shvatanje zubobolje i terapijskih postupaka predstavljaju temelj naše nauke kakvu je danas učimo i znamo. Počev od antičke Grčke, Rima i Renesanse, čiji su se najbistriji umovi bavili problematikom ljudskog bića i time dobili zahvalnost generacija posle njih, do danas kad se očuvanje oralnog zdravlja smatra jednom od važnijih karika zdravog ljudskog organizma. Ovaj naš medicinski članak ima za cilj da sagleda razvoj parodontologije, kao granu stomatologije, uporedi terapiju i shvatanja onih koji su se bavili njom i da na jednom mestu pokuša da sagleda dostignuća stomatološke nauke kakvu je znamo danas.
**Ključne reč:** Istorija lečenja prodontitisa**,** parodoncijum, gingiva, periodoncijum, cement zuba, alveolarna kost, alveola

## UVOD

Parodoncijum (potporni aparat zuba) čine: gingiva, alveolarna kost, periodoncijum i cement korena zuba. To su tkiva koja, pored svojih histoloških razlika, imaju zajedničku funkciju da čvrsto drže zub u alveolarnoj kosti. Danas su dostupni materijalni, pisani i biološki ostaci iz ranijih perioda, pomoću kojih možemo da stvorimo jasniju sliku kako su se shvatanja i nauka razvijala u pogledu lečenja oboljenja parodoncijuma, od najstarijijih vremena do danas.

Građa tkiva parodoncijuma, zbog svoje velike otpornosti omogućava njihovu očuvanost kao biološki materijal za izučavanje ranijih civilizacija. Paleostomatologija ili paleopatologija je posebna disciplina koja se razvila sa ciljem izučavanja tkiva zuba i parodoncijuma [1]. Istoričarima su ova saznanja pomogla u pogledu sagledavanja svakodnevnog života, tegoba, ishrane i vrste lečenja oboljenja parodoncijuma, što je u mnogome objašnjavalo i stepen razvijenosti ranijih civilizacija. Karijes zuba, hipoplazije gleđi zuba, frakture zuba i vilica, komplikacije kao što je apsces su neka od oboljenja koja se mogu naći na iskopanim ostacima kosti lobanja iz vremena praistorije [24]. U drevnoj Mesopotamiji, bavljenje medicinom bilo je regulisano Hamurabijevim zakonikom, koji je najpoznatiji i najstariji pravni spis, ispisan klinastim pismom. Iz njega se može zaključiti da su postojali ljudi koji su se bavili lečenjem tegoba drugih ljudi, hiljadama godina p.n.e. Religija je imala veliki uticaj na stanovništvo u ovom periodu ljudske istorije, a lekari i ljudi drugih profesija su, smatra se, pripadali svešteničkoj klasi. Razlog nastanka mnogih tegoba i bolova prepisivalo se duhovima i demonima. Najčešći način lečenja bio je hirurški. Bolesti očiju, usta i zuba bile su česte, a razlog nastanka karijesa zuba se prepisivao “zubnom crvu”. U sačuvanim pisanim dokumentima su pronađeni i terapijski modaliteti lečenja oboljenja parodoncijuma, koja se najčešće svodila na trljanje zuba određenim melemima, dobijeni mešanjem biljaka, smola i začina. Ovi melemi bi se koristili kod zubobolje i kod labavljenja zuba, a lečenje bi trajalo dok se ne pojavi krvarenje, što se smatralo pozitivnim znakom koji vodi ka izlečenju [16]. U starom Egiptu (3000 godina p.n.e.) medicina se bazirala na religijskim shvatanjima, kao i sama kultura, arhitektura i umetnost. To dokazuju mnogobrojni zapisi na papirusima. Papirus Edvina Smita je najastarije pisano delo o hirurškom lečenju. On sadrži i prve anatomske i patološke opise ljudskog tela, dijagnozu i plan terapije. Prvi put je opisana kauterizacija patološki izmenjenog tkiva i odstranjivanje tumora. Opis ekstrakcije razlabavljenih i čvrstih zuba ukazuju da su lekarima iz ovog doba bila poznata i oboljenja parodoncijuma. U terapiji


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# TREATMENT OF PATIENTS WITH PERIODONTITIS (PERIODONTAL DISEASE) THROUGH HISTORY

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**Summary:** Preserved biological remains of teeth and jaws from prehistoric times, showing signs of periodontal tissue diseases, indicate that these diseases are as old as humanity itself. There are numerous evidence of human interest in oral healthand it dates back centuries ago. The oldest civilizations and their understanding of dental pain and therapeutic procedures form the foundation of the science we learn and know today. Starting from ancient Greece, Rome, and the Renaissance, where the brightest minds tackled human issues, earning the gratitude of generations that followed, to modern times where maintaining oral health is considered one of the vital components of a healthy human organism. This medical article aims to examine the development of periodontology as a branch of dentistry, compare the therapies and perceptions of those who studied it, and attempt to summarize the achievements of dental science as we know it today.

**Keywords:** History of periodontitis treatment, periodontal tissue, gingiva, the periodontal ligament, tooth cement, alveolar bone, alveolus

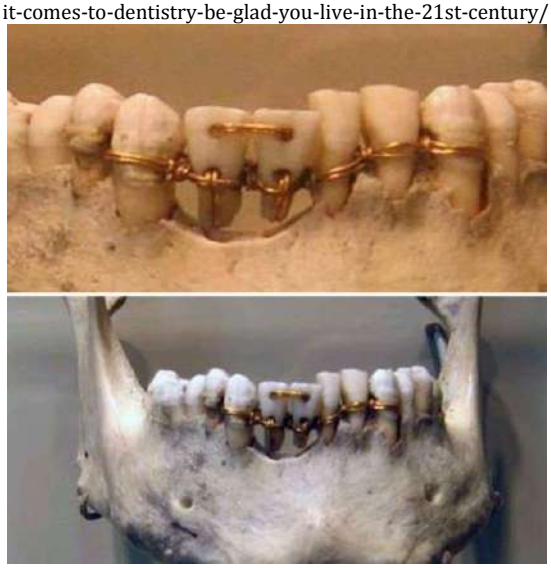
## INTRODUCTUON

The, periodontal tissue (supporting structure of the tooth) consists of the gingiva, alveolar bone, the periodontal ligament, and root cementum. These tissues, despite their histological differences, have a common function: to firmly hold the connection of the tooth within the alveolar bone. Today, material, written and biological remainsfrom earlier periods are available, allowing us to create a clearer imageof how the science evolved regarding the treatment of periodontal diseases, from ancient times to the present.

The structure of periodontal tissues, due to its high resistance, has enabled their preservation as biological material for studying ancient civilizations. Paleostomatology or paleopathology is a specialdiscipline developed with the aim of studying the tissues of teeth and the periodontal tissues [1]. These findings have helped historians understand daily life, nutrition, and treatment methods for periodontal diseases, which largely explain the development level of ancient civilizations. Tooth decay, enamel hypoplasia, tooth and jaw fractures, and complications such as abscesses are among the diseases observed in excavated skull bone remains from prehistoric times [24]. In ancient Mesopotamia, medicine was regulated by Hammurabi's Code, the most famous and oldest legal document written in cuneiform script. From it, we can conclude that people who treated others' ailments existed thousands of years BC. Religion had a significant impact on the population during this period of human history, and doctors and people of other professions were considered to belong to the priestly class. The cause of many diseasesand pains was attributed to spirits and demons. The most common treatment method was surgical intervention. Diseases of the eyes, mouth, and teeth were frequent, and the cause of tooth decay was ascribedto the "tooth worm." Preserved written documents also reveal therapeutic modalities for treating periodontal diseases, which primarily involved rubbing the teeth with specific ointments made by mixing plants, resins, and spices. These ointments were used for toothaches and loosened teeth, and treatment would continue until bleeding occurred, which was considered a positive sign leading to recovery [16]. In ancient Egypt (3000 BC), medicine was based on religious beliefs, as was their culture, architecture and art. This has been proven by numerous writings on papyri. The Edwin Smith Papyrus is the oldest written

obolelog parodoncijuma koristili su se biljni melemi za ublažavanje tegoba i bolova, kao i za učvršćivanje zuba u alveoli. Ti melemi su se sastojali od biljaka, meda, začina i upotrebljavani su utrljavanjem u bolne regije ili u predelu zuba koji su izazivali tegobe [2]. Egipatski pisar Hasi-Re, koji je živeo u vreme 3. egipatske dinastije, bio je prvi zubni lekar u starom Egiptu. Između ostalog, na njegovoj grobnici napisana je titula „najveći među onima koji se bave zubima". Takođe, njemu se pripisuje i to da je bio prva osoba koja je prepoznala oboljenja parodoncijuma [17]. Biološki ostaci iz doba Feničana (2500 godina p.n.e.) ukazuju da je ova civilizacija rešavala probleme razlabavljenih, pa i ispalih zuba, međusobnim vezivanjem zlatnim žicama [3]. (Slika 1.)

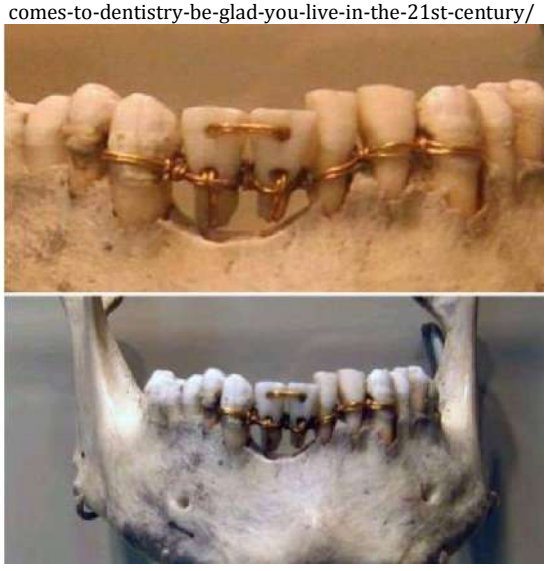
**Slika 1.** Zlatna žičana ligatura korišćena kao terapijski postupak u lečenju labavljenja zuba
preuzeto sa: https://mydesultoryblog.com/2018/10/when-it-comes-to-dentistry-be-glad-you-live-in-the-21st-century/



Najznačajnija ličnost medicine u antičkoj Grčkoj (750-320 p.n.e.) bio je Hipokrat (460-370 p.n.e.). On se i danas smatra ocem medicine, a njegova zakletva se polaže u mnogim zemljama nakon završenih studija medicine i srodnih fakulteta. Njegov doprinos modernoj medicini je višestruk. Između ostalog, uvideo je značaj kliničkog posmatranja i procene pacijenata. Prepoznao je važnost prirode u procesu izlečenja i protivio se terapijskim postupcima koji mogu biti štetni po pacijenta. Uveo je koncept prevencije oboljenja preko zdrave ishrane i zdrave životne sredine. Opisao je iščašenja i prelome vilica kao i ulceracije koje se javljaju u ustima kod sistemskih oboljenja. Jedna od tema kojom se bavio bila je i etiologija oboljenja parodoncijuma, kao i objašnjenje nicanja zuba. Pojavu zapaljenja desni objašnjavao je nagomilavanjem čvrstih naslaga na zubima tj. kamenca i oboljenjima slezine. Kod jednog pacijenta sa obolelom slezinom navodi da ima otečen stomak, akutne bolove i desni koje se odvajaju od zuba i neprijatno mirišu [18]. Pored Hipokrata, Aristotel (384-322 p.n.e.) je bio vodeći naučnik, učitelj i folozof antičke Grčke. Istraživao je etiologiju i pratio simptome oralnih bolesti. Pisao je o oboljenjima parodoncijuma i karijesu zuba, opisivao je morfologiju zuba i sagledao je značaj okluzije. Proučavao je štetno dejstvo šećera i lepljive hrane na zube i tkiva parodoncijuma. Kao jedan od primera ispitivao je dejstvo smokava na zdravlje parodoncijuma. Ukazivao je na njihovu slatkoću i lepljivu strukturu kao uzrok nastanka karijesa i zapaljenja desni. Smatrao je da naslage ostaju u tkivima parodoncijuma i između zuba, na mestima sa kojih je njihovo uklanjanje otežano [4]. U antičkom Rimu, interesovanje lekara je pre svega bilo na prevenciji oboljenja parodoncijuma. U ovom periodu (10.p.n.e.–25.n.e.), oralna higijena je smatrana za važnog činioca zdravlja populacije. U mnogim sačuvanim dokumentima, pominje se i korišćenje četkice za zube i njen značaj [11]. Kao prvi lekar izdvojio se Aulo Kornelije Celzo (25 p.n.e.-10 n.e). U svojim knjigama, u kojima je skupio sva dotadašnja znanja iz medicine, pored značaja prevencije i održavanja oralne higijene, opisao je i različite vrste lečenja oboljenja parodoncijuma. U jednoj od njih, između ostalog, piše da desni koje krvare treba premazivati jabukovim sokom i sirćetom. Opisao je i korišćenje kauterizacije za odstranjivanje uvećanih desni i savetovao da se one posle tog tretmana premazuju medom i crvenim vinom [5]. Zlatno doba islama je period koji se proteže od 8. do 13. veka n.e. Islamski svet je tokom ovog perioda doživeo značajan kulturni, naučni i tehnološki napredak. Iz tog perioda izdvaja se Abulkasis, kao najpoznatiji lekar zapadnog Kalifata. Opisao je hemofiliju, hirurško odstranjivanje tumora sa metastazama, primenu kauterizacije u zaustavljanju krvarenja oštećenog krvnog suda. Shvatio je da su naslage i kamenac na zubima etiološki faktor za nastanak parodontopatija. Razumeo je značaj i potrebu za uklanjanje naslaga, kako na zubima tako i u prostorima ispod desni, što ga je navelo da osmisli i napravi seriju instrumenata kojima bi

work on surgical treatment. It also contains the first anatomical and pathological descriptions of the human body, diagnosis, and treatment plans. The first descriptions of cauterization of pathological tissue and tumor removal are found in this papyrus. Descriptions of extracting loosened and intact teeth indicate that periodontal diseases were known to physicians of that era. In the therapy for diseased periodontal tissue, plant-based ointments were used to reduce discomfort and pain as well as to strengthen the tooth within the alveolus. These ointments were made from plants, honey and spices and applied by rubbing them into painful areas or near the teeth causing discomfort [2]. The Egyptian scribe Hesy-Ra, who lived during the time of the 3rd Egyptian dynasty, was the first dental physician in ancient Egypt. Among other things, his tomb bears the title "the greatest among those who deal with teeth." He is also credited with being the first person to recognize periodontal diseases [17]. Biological remains from the Phoenician period (2500 BC) indicate that this civilization was aware ofthe issues of loosened and even lost teeth. One of the methods they used for solving this problem is by binding the loosened teeth together with gold wires [3]. (Figure 1.)

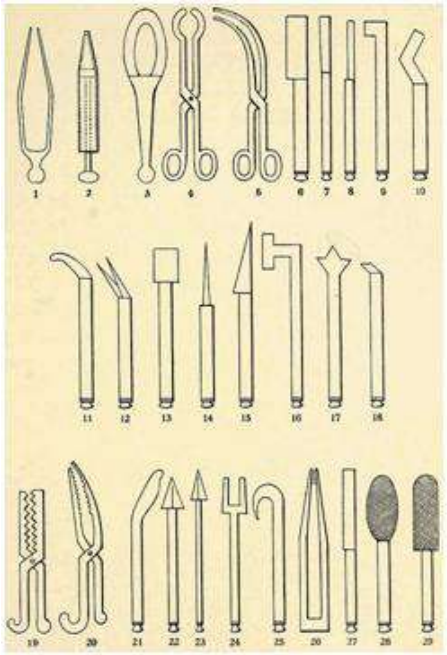
**Figure 1.** Golden wire ligature used as a therapeutic procedure in the treatment of tooth loosening
Source: https://mydesultoryblog.com/2018/10/when-it-comes-to-dentistry-be-glad-you-live-in-the-21st-century/



The most prominent figure in medicine in ancient Greece (750–320 BC) was Hippocrates (460–370 BC). He is still considered as the father of medicine, and his oath is taken in many countries after completing studies in medicine and relatedmedical fields. His contribution to modern medicine iswell known. Among other things, he recognized the importance of clinical observation and patient evaluation. He spoke aboutthe role of nature in the healing process and opposed therapeutic methods that could harm the patient. Hippocrates introduced the concept of disease prevention through a healthy diet and healthy environment. He described jaw dislocations and fractures as well as ulcers occurring in the mouth due to systemic diseases. One of the topics he dealt withwas the etiology of periodontal diseases, along with an explanation of tooth eruption. He attributed gum inflammation to the accumulation of hard deposits on teeth (i.e. tartar) and spleen diseases. In one patient with a spleen disease, he noted a swollen abdomen, acute pain and gums that separated from the teeth with an unpleasantsmell [18]. In addition to Hippocrates, Aristotle (384–322 BC) was a leading scientist, teacher and philosopher in ancient Greece. He researched the etiology and observed symptoms of oral diseases. Aristotle wrote about periodontal diseases and tooth decay, described the morphology of teeth and considered the importance of occlusion. He studied the harmful effects of sugar and sticky foods on teeth and periodontal tissues. As an example, he examined the impact of figs on periodontal health, pointing out their sweetness and sticky texture as causes of cavities and gum inflammation. Aristotle believed that deposits remained in periodontal tissues and between teeth, in areas where their removal was difficult [4]. In ancient Rome, physicians primarily focused on preventing periodontal diseases. During this period (10 BC–25 AD), oral hygiene was considered an important factor in public health. Many preserved documents mention the use of toothbrushes and their significance [11]. The first prominent physician was Aulus Cornelius Celsus (25 BC–10 AD). In his books, which contained all existing knowledge of medicine at that time, he described various treatments for periodontal diseases alongside the significance of prevention and oral hygiene. In one of his works, he wrote that bleeding gums should be treated with apple juice and vinegar. He also described using cauterization to remove enlarged gums and advised applying honey and

se te naslage uspešno uklanjale. Ti instrumenti su preteče današnjih stomatoloških kireta [15]. (Slika 2.)

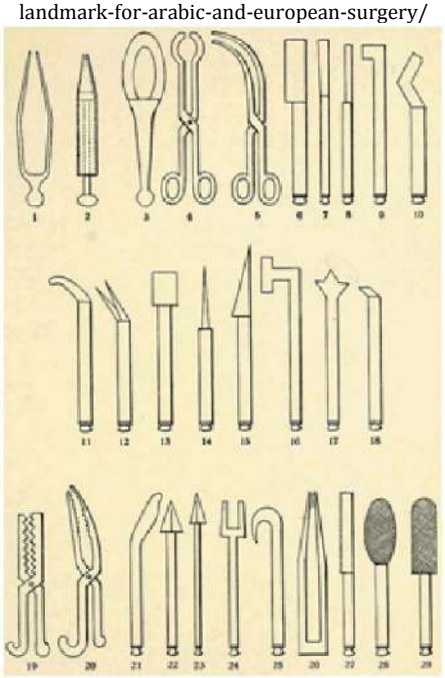
**Slika 2.** Skice parodontalnih instrumenata koje je dizajnirao Abulkasis
preuzeto sa:
https://medheritage.org/2023/03/01/abulcasis-a-landmark-for-arabic-and-european-surgery/



Period Renesanse daje novi zamah u umetnosti, kulturi, medicini, pa samim tim i stomatologiji. Nastaju knjige i spisi koji opisuju, temeljitije nego do tada, anatomiju čoveka, što je rezultat usavršenijih metoda disekcije kadavera [6]. Pronalazak štamparije omogućio je štampanje knjiga u većem broju primeraka. A prevođenje medicinskih knjiga doprinelo je širenju znanja iz oblasti medicine. Bavljenje naukom i istraživački poziv je postao pristupačniji i mnogi su iskoristili tu šansu. Prva štampana knjiga iz oblasti stomatologije objavljena je 1530. godine pod nazivom „Mala medicinska knjiga za sve vrste bolesti i nemoći zuba" (*Little Medicinal Book for All Kinds of Diseases and Infirmities of the Teeth*) od Artzneja Buklajna. Ona je sadržala opis mnogih dotadašnjih saznanja, terapijskih metoda i iskustava lekara iz antičke Grčke i Rima, kao i zapažanja i iskustva arapskih lekara u periodu Zlatnog doba Islama. U nekoliko poglavlja ove knjige opisana su i oboljenja gingive i parodoncijuma [7]. Bartolomeo Eustahio (1500-1574), italijanski naučnik, dao je veliki doprinos medicinskoj nauci, posebno iz oblasti anatomije čoveka. Pored preciznih opisisa građe zuba i pulpe, opisao je i oboljenja koja zahvataju usnu šupljinu i ponudio načine njihovog lečenja. Njegovo lečenje parodontitisa odnosno parodontopatija, bilo je, za to vreme, izuzetno moderno. Savetovao je uklanjanje zubnog kamenca i odstranjivanje patološki izmenjenog tkiva [9]. Hirurške procedure na oralnim tkivima predstavljaju predmet njegovih daljih istraživanja. Ambroaz Pere (1510-1590) je prvi dao opis oralnohirurških i nekih drugih zahvata, pa je zato smatran najvećim hirurgom Renesanse. Usavršio je mnoge hirurške instrumente za oralnohirurške zahvate. Shvatio je značaj zubnog kamenca u etiologiji oboljenja gingive i parodoncijuma i ukazao na neophodnost njegovog uklanjanja [8]. U 18.veku ističu se dva imena od posebnog značaja za dalji razvoj parodontologije: Pjer Fošar i Džon Hanter. Fošar, ratni hirurg francuske mornarice, interesovao se posebno za oboljenja usne duplje mornara na brodovima. Oboljenje koje je najviše zadavalo problema mornarima, bio je skorbut. Za njegove veštine se brzo saznalo i on ubrzo postaje renomirani i veoma poznat. Uspešno je rešavao probleme karijesa zuba, kamenca i uklanjanja beningnih tumora usne duplje. Njegov značaj je i u tome, što je 1742. godine prvi opisao i uradio gigivektomiju, proceduru kojom je uklonio višak tkiva gingive. U svojim knjigama, detaljno opisuje anantomiju gingive, njene promene u građi i strukturi i epulise [15]. Džon Hanter, britanski lekar i naučnik, detaljno je analizirao i izučavao anatomiju čoveka. Tokom svog života skupio je preko 13 000 anatomskih uzoraka, koje je izučavao i opisivao u svojim publikacijama. Svoje rukopise u kojima opisuje anatomiju glave upotpunio je ilustracijama kostiju vilica i lica, kao i mlečnih i stalnih zuba. Opisao je i morfologiju zuba sa kanalima korenova i tkivom pulpe (Slika 3.). Kao hirurg, smatrao je da sva oboljenja i promene na koštanim i mekim tkivima usne duplje treba da budu tretirana od strane hirurga. Pratio je napredovanje karijesa zuba, opisivajući „bela tačkasta polja" na zubu koja kasnije progrediraju u mrka polja koja predstavljaju razoreno tkivo zuba. Opisuje i „džepove" u kosti i njihov uticaj na njenu destrukciju koja dovodi do rasklaćenja zuba [10].

red wine to the area after the procedure [5]. The Islamic Golden Age, spanning from the 8th to 13th centuries AD, marked significant cultural, scientific, and technological advancements in the Islamic world. Among the notable figures of this era was Abulcasis, the most renowned physician of the western Caliphate. He described hemophilia, surgical removal of metastasized tumors and the use of cauterization to stop bleeding from damaged blood vessels. Abulcasisrealized that deposits and tartar on teeth were etiological factors in the development of periodontal diseases. He understood the importance of removing deposits from both the teeth and spaces beneath the gums, leading him to design and create a series of instruments for effectively removing these deposits. These instruments were the forerunners of modern dental scalers and curettes [15]. (Figure 2.)

**Figure 2.** Sketches of periodontal instruments designed by Abulcasis
Source: https://medheritage.org/2023/03/01/abulcasis-a-landmark-for-arabic-and-european-surgery/



The Renaissance brought new momentum to art, culture, medicine and dentistry. Books and writings emerged, describing human anatomy more thoroughly than before, thanks to advancements in dissection methods [6]. The invention of the printing press enabled the production of books in greater numbers and the translation of medical texts contributed to the spreadingof medical knowledge. The pursuit of science and research became more accessible and many took advantage of this opportunity.The first printed book in the field of dentistry was published in 1530 under the title "Little Medicinal Book for All Kinds of Diseases and Infirmities of the Teeth" by ArtzneyBuchlein. It included descriptions of previously known information, therapeutic methods and the experiences of physicians from ancient Greece and Rome, as well as observations and knowledge from Arab physicians during the Islamic Golden Age. Several chapters of this book discussed diseases of the gingiva andperiodontal tissue [7]. Bartolomeo Eustachio (1500–1574), an Italian scientist, made significant contributions to medical science, particularly in human anatomy. Alongside detailed descriptions of tooth structure and pulp, he described oral diseases and offered treatment methods. His approach to treating periodontitis and periodontal disease was considered modern for that era. He advised the removal of dental tartar and excision of pathologically altered tissue [9]. Surgical procedures on oral tissues were the subject of his further research.AmbroiseParé (1510–1590) was the first to describe oral surgical and other procedures, earning recognition as the greatest surgeon of the Renaissance. He refined numerous surgical instruments for oral procedures and understood the importance of tartar in the etiology of gingival and periodontal diseases, emphasizing the necessity of its removal [8]. In the 18th century, two names stand out as particularly significant for the further development of periodontology: Pierre Fauchard and John Hunter. Fauchard, a French navy warsurgeon, was particularly interested in oral diseases affecting sailors aboard ships. The condition that caused the most trouble among sailors was scurvy. His skills became widely known and he soon gained fame. He successfully was treatingdental cavities, tartar issues and the removal of benign tumors in the oral cavity. Fauchardis notable for performing the first gingivectomyprocedure in 1742, a method for removing excess gingival tissue. In his books, he detailed the anatomy of the gingiva, changes in its structure and morphology, and epulides [15]. John Hunter, a British physician and scientist, whoanalyzed in detail and studied human anatomy. During his lifetime, he collected over 13,000 anatomical specimens, which he studied

**Slika 3.** Knjiga Džona Hantera iz 1771. godine
preuzeto sa: - https://www.rcseng.ac.uk/library-and-publications/library/blog/john-hunter-the-natural-history-of-the-human-teeth-1771/


**Devetnaesti vek** bio je period velikih medicinskih otkrića i dostignuća. Istraživanja iz oblasti patologije i mikrobilologije, otkriće anestezije i iks-zraka, promenila su koncept dijagnostike i poboljšala terapiju oralnih oboljenja. Nemačka i Amerika uzimaju vodeću poziciju u istaraživanju i unapređenju kliničkih terapijskih procedura. Vodeći lekar koji se bavio oboljenjima parodoncijuma i njegovim lečenjem bio je Džon Rigs (1811-1855). Njegova interesovanja za gingivu i njena oboljenja javila su se još na početku njegovog kliničkog rada. Zbog svoje uspešnosti u dijagnostici i terapiji, ali i odluke da svoj klinički i naučni rad usmeri samo na oboljenja tkiva parodoncijuma, smatra se prvim parodontologom u istoriji. Njegov značaj u lečenju i poznavanju oboljenja parodoncijuma objašnjava i činjenica da se oboljenje koje se danas prepoznaje kao parodontopatija, tada nazivalo „Rigsova bolest" [11]. Protivio se hirurškoj resekciji gingive, postupku koji je do tada najčešće primenjivan u terapiji, a insistirao je na odstranjivanju patološkog tkiva posebno u subgingivalnoj regiji. Veliku pažnju pridavao je prevenciji i značaju oralne higijene, odnosno pranju zuba. Lenard Koker (1785-1850), zubni lekar i istraživač, takođe je igrao značajnu ulogu u razvoju parodontologije u 19. veku. Njegova razmišljanja i inovativne ideje, promenila su pogled na dotadašnja znanja o oboljenjima parodoncijuma. Pregledom i praćenjem pacijenata, primetio je da oboljenja parodoncijuma počinju inflamacijom desni koje opisuje kao „sporo progredirajuće oboljenje". Čvrste naslage na zubima je označio kao važan etiološki faktor za početak oboljenja. Insistirao je na redovnosti pranja zuba, posle svakog obroka, četkicom za zube. Tema kojom se bavio bila je i „fokalna infekcija". Predlagao je da se zubi sa lošom prognozom i zaostali korenovi zuba izvade, radi sprečavanja nastanka oboljenja udaljenih organa [21]. U **dvadesetom veku** došlo je do kontinuiranog razvoja nauke i tehnologije. Razlog tome su i ratovi koji su se vodili u ovom periodu istorije. Težnja za moći i savladavanju protivnika, zahtevala je uključenost najbistrijih umova ovog doba iz svih oblasti društva i nauke. Otkrivanjem antibiotika, uspešno su se lečile mnoga, do tada teška oboljenja infektivne prirode. Upotreba rendgena i magnetne rezonance unapredila je preciznost dijagnostike i otvorila vrata jednoj inovativnoj i novoj terapijskoj proceduri - transplantaciji organa. Stomatologija je pratila napredak i razvoj tehnoloških i naučnih dostignuća u medicini. Posle vojne medicine, korišćenje rendgena kao pomoćnu dijagnostičku proceduru, uvodi i stomatologija [12]. (Slika 4.). Umesto ručnih stomatoloških instrumenata, počeli su da se koriste mašinski instrumenti na električni pogon. Dizajnirane su i prve stomatološke stolice sa reflektorima. Lokalna anestezija je počela da se koristi prilikom intervencija. Otkrićem preventivne uloge fluorida u nastanku karijesa, unapredilo se oralno zdravlje i prevenirala pojava oboljenja zuba i parodoncijuma. Dizajnirani su novi parodontološki instrumenti koji su potpomogli dijagnostikovanju i lečenju oboljenja parodoncijuma. Dizajnirana je i prva parodontološka sonda, tada nazivana parodontometar, čije korišćenje je omogućilo bolju dijagnostiku parodontalnih džepova i merenje njegove dubine. Dimenzije, koje bi se dobile na kontrolnim pregledima, su evidentirane. Time bi lekar mogao da prati rezultat svog terapijskog postupka [13]. Pored kauzalne, nehirurške terapije parodoncijuma i hirurške terapijske procedure doživele su svoju renesansu. Za razvoj parodontalne hirurgije u ovom periodu, najviše su zaslužni Robert

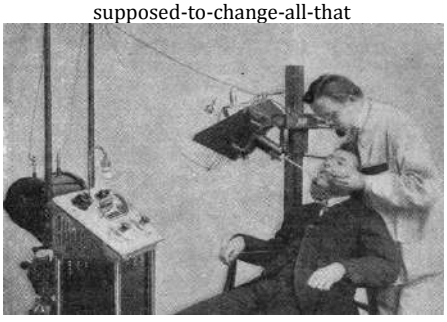
and described in his publications. His manuscripts on head anatomy were supplemented with illustrations of jaw and facial bones, as well as primary and permanent teeth. Hunter also described the morphology of teeth with root canals and pulp tissue (Figure 3). As a surgeon, he believed that all diseases and changes in the bony and soft tissues of the oral cavity should be treated by surgeons. He tracked the progression of dental cavities, describing “white spot fields” on teeth that later advanced to brown areas representing decayed tooth tissue. Hunter also described "pockets" in the bone and their destructive effects, leading to tooth loosening [10].

**Figure 3. The book by John Hunter from the year 1771**
Source: - https://www.rcseng.ac.uk/library-and-publications/library/blog/john-hunter-the-natural-history-of-the-human-teeth-1771/


**The 19th century** was a period of great medical discoveries and advancements. Research in pathology and microbiology, the discovery of anesthesia and X-rays revolutionized diagnostic concepts and improved the treatment of oral diseases. Germany and America took leading roles in clinical therapeutic procedures and research. John Riggs (1811–1855) was a prominent physician who focused on periodontal diseases and their treatment. His interest in gingiva and its diseases began early in his clinical career. Due to his success in diagnosis and treatment, as well as his decision to dedicate his clinical and scientific work entirelyto periodontal tissue diseases, Riggs is considered the first periodontistin history. His importance in understanding and treating periodontal diseases is highlighted by the fact that the disease now recognized as periodontitis was once called "Riggs' disease." [11]. Riggs opposed gingival surgical resection, a procedure widely used at the timeand insisted on removing pathological tissuein the subgingivalregion. He emphasized the importance of prevention and oral hygiene, particularly tooth brushing. Leonard Koecker (1785–1850), a dentist and researcher, also played a significant role in the development of periodontology in the 19th century. His observations and innovative ideas reshaped the understanding of periodontal diseases. By examining and following patients, he noticed that periodontal diseases begin with gingival inflammation, which he described as "slowly progressing." He identified hard deposits on teeth as a critical etiological factor in disease onset and emphasized the necessity of regular tooth brushing after meals. Koeckeralso addressed the concept of "focal infection," suggesting that teeth with poor prognosis and retaineddental roots should be extracted to prevent diseases in distant organs [21]. The 20th century saw continuous development in science and technology, partly influenced by the wars of this era. The pursuit of power and overcoming adversaries required the involvement of the brightest minds across all fields. The discovery of antibiotics led to successful treatments for numerous infectious diseases. The use of X-rays and magnetic resonance improved diagnostic accuracy and opened doors to innovative therapeutic procedures, such as organ transplants. Dentistry followed medical advancements, integrating technological and scientific achievements. Following military medicine, dentistry adopted X-rays as a diagnostic tool [12] (Figure 4). Machine-powered dental instruments began replacing manual ones, and dental chairs with reflectors were designed. Local anesthesia started being used during interventions. The discovery of fluoride's preventive role in cavity formation improved oral health and prevented dental and periodontal diseases. New periodontal

Njuman i Lenard Vidman. Vidmanov režanj iz 1918. označio je prekretnicu u daljem napredovanju parodontalne hirurgije. Ova, u to vreme, inovativna hirurška metoda bila je karakteristična po trapezoidnom obliku režnja, sa dve vertikalne relaksacione incizije, što veću mobilnost režnja i bolji pristup patološkom tkivu [19]. Deceniju kasnije, 1931. Kirkland uvodi novi inovativni pristup koji će biti nazvan „otvorena subgingivalna kiretaža“. Ovom procedurom, insistira se na očuvanju zdravog prodontalnog tkiva i suzbijanje inflamacije, a kiretažom režnja bi se uklonilo inflamirano i patološki izmenjeno tkivo [20]. Nakon Drugog svetskog rata, nova generacija naučnika i kliničara preuzela je ulogu svojih prethodnika. Svet koji je pretrpeo velike gubitke, u svakom pogledu počeo je da se okreće inovativnim rešenjima i gradnji novog ljudskog društva. Briga o ljudima i njihovim problemima postali su normativ društva. Oralno zdravlje stanovništva, u SAD, pokazalo je kontinuirano poboljšanje zahvaljujući preventivnim merama koje su uvedene. Hirurške procedure na parodoncijumu počele su sve šire da se primenjuju, a i stalno se ulagalo u nove materijale i instrumente. Novitet u lečenju oboljenja parodoncijuma predstavljao je početak lokalne upotrebe penicilina. On bi se u obliku pastila davao pacijentima, a spora razgrdanja osiguravala je njegovu dugotrajnu koncentraciju u usnoj duplji. Indikacije su bile: akutni ulcerativni gingivostomatitis, akutni streptokokni tonzilitis. Primenjivao se i preventivno pre određenih oralnohirurških intervencija i kod pacijenata sa nekim sistemskim oboljenjima. Kasnije je penicilin, kao lek izbora, počeo da se daje i intramuskularno kod pacijenata sa akutnim i nekrotizirajućim promenama na gingivi [14].

**Slika 4.** Prvi komercijalni dentalni rendgen aparat (1905. godina)
preuzeto sa:
https://paleofuture.com/blog/2016/8/30/going-to-the-dentist-in-1909-was-a-nightmare-but-x-rays-were-supposed-to-change-all-that

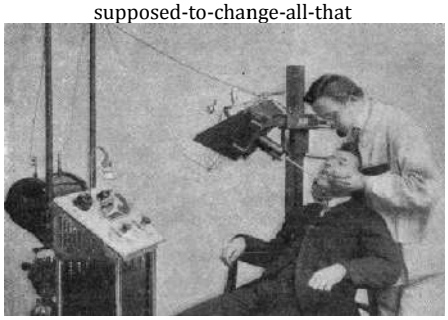


Ovaj period obeležava i rađanje nove stomatološke discipline - implantologije. Ideja da se izvađeni zub zameni drugim zubom ili materijalom, datira još od perioda najstarijih ljudskih civilizacija (Slika 5.). Tek u 20. veku implantologija počinje da se razvija kao nauka. Prekretnicu u implantološkoj terapiji predstavlja otkriće švedskog ortopedskog hirurga Brenemarka. On je, prilikom jedne hirurške intervencije, koristio biokompatibilne titanijumske intraosealne implantate i kasnije je opisao termin „osifikacija“ koji će postati temelj savremene implantologije [22].

Danas, lečenje obolelog parodoncijuma zahteva temeljan pristup, vrlo precizne analize i sagledavanje svih mogućih rezultata primenjene iz terapije. Parodontolozi, osim što leče oboljenja potpornog aparata zuba, sagledavaju i njihov uticaj na čitav organizam. Oboljenja parodoncijuma (parodontitis) mogu da utiču na zdravlje mnogih sistema i organa. Sa druge strane mnoga sistemska oboljenja daju svoje manifestacije u usnoj duplji. Savremena parodontalna hirurgija, pored modifikovanih i poboljšanih hirurških procedura i implantologije, teži i regenerativnom i rekonstruktivnom pristupu lečenja. Pre bilo koje intervencije, insistira se na detaljnom pregledu, proceni stanja parodoncijuma i planiranju terapijskih procedura. Za tu svrhu danas se koriste mnogobrojni kompijuterski programi koji omogućavaju kliničaru da na trodimenzionalnom modelu isplanira odgovarajuće lečenje i proceni uspešnost primenjene terapije. Istraživanja iz oblasti regenerativnih hirurških procedura i biomaterijala, dovela su do težnje kliničara da njima nadoknade originalna izgubljena tkiva parodoncijuma, čime bi se pacijentu povratila funkcija i morfologija potpornog aparata zuba. Istraživanja iz oblasti matičnih ćelija omogućila su povećanje uspešnosti regenerativne i rekonstruktivne terapije uznapredovalih oboljenja parodoncijuma, a sve hirurške procedure su izmenjene tako da budu minimalno invazivne uz što veći procenat očuvanja zdravog tkiva parodoncijuma [23].

instruments were created to aid in diagnosing and treating periodontal diseases. The first periodontal probe, then called a "periodontometer", was designed, allowing better diagnosis of periodontal pockets and measurement of their depth. Measurements recorded during follow-ups enabled dentists to monitor treatment outcomes [13]. Both causal, non-surgical therapy and surgical procedures of the periodontal tissueunderwent itsrenaissance. Robert Newman and Leonard Widmanwere pivotal figures in the development of periodontal surgery during this period. Widman's flap procedure from 1918 marked a breakthrough in periodontal surgical advancements. This innovative method featured a trapezoidal flap shape with two vertical relaxation incisions, providing greater mobility and better access to pathological tissue [19]. A decade later, in 1931, Kirkland introduced a new approach called "subgingival open-field curettage." This procedure aimed to preserve healthy periodontal tissue and suppressinflammation, by removinginflamed and pathologically altered tissue [20]. Post-World War II, a new generation of scientists and clinicians took over the role from their predecessors. A world recovering from significant losses began focusing on innovative solutions and rebuilding society. Caring for people's needs became a societal norm. In the U.S., oral health improved continuously thanks to preventive measures introduced. Surgical procedures for the periodontal tissuebecame increasingly widespread, with investments made in new materials and instruments. A notable development in treating periodontal diseases was the local use of penicillin. Administered in lozenge form, its slow breakdown ensured prolonged concentration in the oral cavity. Indications included acute ulcerative gingivostomatitisand acute streptococcal tonsillitis. Penicillin was also used preventively before certain oral surgical interventions and in patients with systemic diseases. Later, penicillin became the drug of choice for intramuscular administration in patients with acute and necrotizing gingival changes [14].

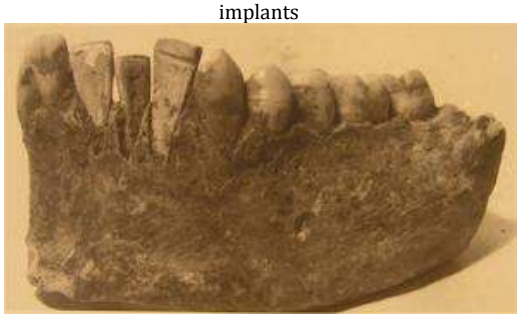
**Figure 4.** The first commercial dental X-ray machine (1905)
Source: https://paleofuture.com/blog/2016/8/30/going-to-the-dentist-in-1909-was-a-nightmare-but-x-rays-were-supposed-to-change-all-that



This period also marks the birth of a new dental discipline – implantology. The idea of replacing an extracted tooth with another tooth or material dates back to the earliest human civilizations (Figure 5). However, it was not until the 20th century that implantologybegan to develop as a science. A major breakthrough in implantologytherapy was the discovery by Swedish orthopedic surgeon Brånemark. During one surgical procedure, he used biocompatible titanium intraosseousimplants and later described the term "osseointegration," which became the foundation of modern implantology [22].

Today, the treatment of diseased periodontal tissuerequires a thorough approach, precise analyses, and consideration of all potential outcomes of the applied therapy. Periodontistsnot only treat diseases of the tooth-supporting structure but also assess their impact on the entire body. Periodontal diseases (periodontitis) can affect the health of many systems and organs, while on the other hand, numerous systemic diseases manifest their signsin the oral cavity.Modern periodontal surgery, besides modified and improved surgical procedures and implantology, strives for a regenerative and reconstructive approach to treatment. Prior to any intervention, emphasis is placed on a comprehensive examination, evaluation of theperiodontal tissue, and the planning of therapeutic procedures. For this purpose, numerous computer programs are now utilized, enabling clinicians to plan appropriate treatments and evaluatethe success of the applied therapy using three-dimensional models.Research in regenerative surgical procedures and biomaterials has led clinicians to aim to restore original lost periodontal tissues, thereby returning function and morphology to

**Slika 5.** Mandibula iz perioda Maja, sa tri implantirana komada ljuske školjke u bezubom prostoru
preuzeto sa: https://dreamdentalimplants.com/history-of-implants



## ZAKLJUČAK

Današnja, savremena parodontologija, nema mnogo sličnosti sa načinima lečenja koji su se praktikovali u ranijih vekova. Jedna od malobrojnih sličnosti predstavlja to da oboljenja parodoncijuma predstavljaju problem sa kojim se i dalje bori ljudski rod. Krvarenje desni, bol, labavljenje zuba, samo su neki od znakova koji su naterali ranije civilizacije da tragaju za rešenjima ovog problema. Zbog toga, od ogromnog značaja za razumevanje razvoja parodotologije, predstavljaju i istorijski podaci. Danas je parodontologija veoma napredovala i obuhvata čitav niz oblasti počev od dijagnoze do nehirurške terapije, pa preko okluzalne terapije, resektivnih i procedura regeneracije tvrdih i mekih tkiva potpornog aparata zuba.

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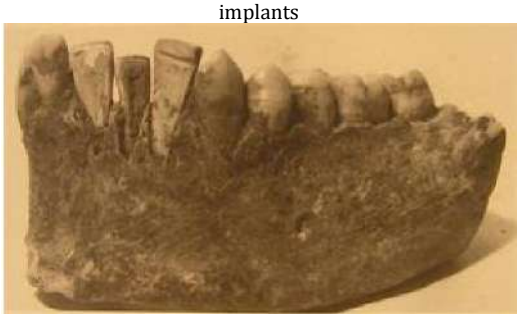
the tooth-supporting structures. Stem cell research has increased the success rate of regenerative and reconstructive therapies for advanced periodontal diseases. All surgical procedures have been adapted to be minimally invasive, with a focus on preserving as much healthy periodontal tissue as possible [23].

**Figure 5.** Mandible from the Mayan period , with three implanted pieces of shell in a toothless space
Source: https://dreamdentalimplants.com/history-of-implants



## CONCLUSION

Modern periodontology has little in common with the treatment methods practiced in past centuries. One of the few similarities is that periodontal diseases continue to be a challenge for humanity. Bleeding gums, pain, and tooth loosening are just some of the symptoms that drove earlier civilizations to search for solutions to this problem. For this reason, historical data is of great importance in understanding the development of periodontology. Today, periodontology has advanced significantly and encompasses a wide range of areas, starting from diagnosis and non-surgical therapy to occlusaltherapy, resectiveprocedures and the regeneration of hard and soft tissues of the tooth-supporting structures.

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# DOKTORKA SMILjA KOSTIĆ – ŽIVOT I DELO ZABORAVLjENE HEROINE

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**Sažetak rada:** Doktorka Smilja Kostić bila je pionir u oblasti medicine, sa velikim doprinosom naročito u oblasti imunologije i infektivnih bolesti. Jedna od njenih najvažnijih misija bila je suzbijanje zaraznih bolesti, koje su u prvoj polovini 20. veka bile jedan od vodećih uzroka mortaliteta u Jugoslaviji. Za vreme Balkanskih ratova Smilja se, kao sedamnaestogodišnja gimnazijalka, dobrovoljno prijavila za bolničarku u Trećoj rezervnoj bolnici u Beogradu. Zbog svoje velike humanosti i hrabrosti koje je pokazala u Balkanskim ratovima, odlikovana je Krstom milosrđa i Bronzanom medaljom srpskog Crvenog krsta. Studije medicine započela je 1915. godine u Lozani, koje je nastavila u Monopelјeu, a diplomirala je 1919. godine u Strazburu. Po završetku studija vratila se u Beograd. Postala je prva žena docent Medicinskog fakulteta u Beogradu. Jedno od njenih najvažnijih dostignuća bilo je uvođenje BCG vakcine u našu zemlju. Za svoj izuzetan doprinos u borbi protiv tuberkuloze odlikovana je Nacionalnim ordenom Legije časti od strane Francuske. U posleratnom periodu nije bila deo ni jedne ideološke organizacije zbog čega je bila označena da ispoljava neprijateljski stav prema socijalističkoj zajednici. Prevremeno je penzionisana i udaljena sa fakulteta. Pola veka nakon udaljavanja sa fakulteta i dvadeset godina nakon smrti, moralno je rehabilitovana. Doktorka Kostić bila je mnogo više od lekara i naučnika. Bila je humanista, lider i vizionar, čiji je uticaj nadmašio granice medicine.
**Ključne reči**: žena, lekar, pionir, dostignuća, vakcina, tuberkuloza

## UVOD

U svetu, u periodu nakon Drugog svetskog rata, BCG vakcina postaje široko prihvaćena preventivna mera protiv tuerkuloze. Naša zemlja bila je među zemljama koje su se intenzivno podvrgle ovoj preventivi, a doktorka koja je dala nemerljiv doprinos u njenoj primeni na našim prostorima bila je odlikovana Legijom časti. Šira javnost je tek 2020. godine saznala da je reč o doktorki Smilji Kostić [1,2]. Doktorka Smilja Kostić bila je pionir u oblasti medicine, sa velikim doprinosom naročito u oblasti imunologije i infektivnih bolesti. Rođena u Beogradu u prvoj polovini 20. veka, doktorka Kostić je svoj život posvetila unapređenju medicinskih saznanja i zdravstvene zaštite, što ju je učinilo jednom od najcenjenijih ličnosti u naučnoj zajednici.

Jedna od njenih najvažnijih misija bila je suzbijanje zaraznih bolesti, koje su u to vreme bile jedan od vodećih uzroka mortaliteta u Jugoslaviji. Sa razvojem nauke i tehnike, doktorka Kostić je bila među prvima koji su u našoj zemlji počeli da proučavaju imuni sistem i njegove odgovore na različite patogene. Njena istraživanja i praktičan rad na terenu značajno su unapredili razumevanje o načinima prevencije i kontrole širenja zaraznih bolesti, čime je pomogla u očuvanju zdravlja čitave zajednice.

U naučno-istraživačkom radu, doktorka Kostić bila je poznata po inovativnom pristupu i velikoj predanosti. Pored rada sa pacijentima, intenzivno se bavila i edukacijom mladih medicinskih radnika, verujući da je obrazovanje ključ za dugoročno poboljšanje zdravstvenog sistema. Osnovala je i nekoliko centara za istraživanje imunoloških reakcija, gde je radila na razvoju novih terapijskih metoda i prevenciji oboljenja [3,4,5].

Rad doktorke Kostić ima veliki značaj i danas, jer su njena otkrića i metodologije postavili temelje za dalji razvoj imunologije i infektologije u Srbiji i šire. Njeno nasleđe živi kroz generacije lekara i istraživača koji nastavljaju njenu misiju, koristeći njene nalaze i


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# DOCTOR SMILJA KOSTIĆ – LIFE AND LEGACY OF A FORGOTTEN HEROINE

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**Abstract:** Doctor Smilja Kostić was a pioneer in the field of medicine, making significant contributions, particularly in the areas of immunology and infectious diseases. One of her most important missions was combating infectious diseases, which were among the leading causes of mortality in Yugoslavia during the first half of the 20th century. During the Balkan Wars, at the age of seventeen, Smilja volunteered as a nurse at the Third Reserve Hospital in Belgrade. Her exceptional humanity and bravery during the Balkan Wars earned her the Cross of Mercy and the Bronze Medal of the Serbian Red Cross. She began her medical studies in 1915 in Lausanne, continued them in Montpellier, and graduated in 1919 in Strasbourg. After completing her studies, she returned to Belgrade, where she became the first female docent at the Faculty of Medicine in Belgrade. One of her most notable achievements was the introduction of the BCG vaccine to the country. For her outstanding contributions to the fight against tuberculosis, she was awarded the National Order of the Legion of Honor by France. In the post-war period, she remained unaffiliated with any ideological organization, which led to accusations of harboring a hostile attitude toward the socialist community. As a result, she was prematurely retired and dismissed from the faculty. Half a century after her dismissal and twenty years after her death, she was posthumously rehabilitated. Doctor Kostić was much more than a physician and scientist. She was a humanist, a leader, and a visionary whose influence transcended the boundaries of medicine.
**Keywords:** woman, physician, pioneer, achievements, vaccine, tuberculosis

## INTRODUCTION

n the world, in the period after the Second World War, the BCG vaccine became widely accepted as a preventive measure against tuberculosis. Our country was among those that actively implemented this prevention, and the doctor who made an immeasurable contribution to its application in our region was awarded the Legion of Honour. The broader public only learned in 2020 that this doctor was Dr. Smilja Kostić [1,2].

Dr. Smilja Kostić was a pioneer in the field of medicine, with significant contributions, especially in immunology and infectious diseases. Born in Belgrade in the first half of the 20th century, Dr. Kostić devoted her life to advancing medical knowledge and healthcare, which made her one of the most respected figures in the scientific community.

One of her most important missions was the control of infectious diseases, which at that time were among the leading causes of mortality in Yugoslavia. With the development of science and technology, Dr. Kostić was among the first in our country to study the immune system and its responses to various pathogens. Her research and practical fieldwork significantly improved the understanding of methods for preventing and controlling the spread of infectious diseases, thereby helping to safeguard the health of the entire community.

In scientific research, Dr. Kostić was known for her innovative approach and great dedication. In addition to working with patients, she was actively involved in educating young medical professionals, believing that education was key to long-term improvement of the healthcare system. She also founded several centers for the study of immunological responses, where she worked on developing new therapeutic methods and disease prevention strategies [3,4,5].

metode u svakodnevnoj borbi za zdravlje ljudi. Kroz posvećenost i strast prema nauci, doktorka Smilja Kostić ostavila je dubok i trajan trag u polju medicine, a njen rad i danas inspiriše.

**RANO DETINJSTVO I OBRAZOVANJE**

Doktorka Smilja Kostić rođena je kao Smilja Joksić 1895. godine u Beogradu, od oca Momčila Joksića, ađutanta Kraljeve garde i majke Stake Pačić. Rođena je kao drugo dete od ukupno sedmoro dece koliko su Momčilo i Staka imali. Praunuka je Tome Vučića Perišića, učesnika Prvog i Drugog srpskog ustanka i najuticajnijeg čoveka u Srbiji u drugoj polovini 19. veka. Pretpostavlja se da je od pradede nasledila upornost, borbenost i veštinu ophođenja sa ljudima, posebno sa decom.

Njeno školovanje nije bilo lako, niti se odigravalo kontinuirano. Osnovnu i srednju školu završila je u Beogradu i takozvani ispit zrelosti položila je 1913. godine. Za vreme Balkanskih ratova (1912-1913) Smilja se, kao sedamnaestogodišnja gimnazijalka, dobrovoljno prijavila za bolničarku u Trećoj rezervnoj bolnici u Beogradu. Zbog svoje velike humanosti i hrabrosti koje je pokazala u Balkanskim ratovima, odlikovana je Krstom milosrđa i Bronzanom medaljom srpskog Crvenog krsta.

Studije medicine započela je 1915. godine u Lozani, tokom teških ratnih godina. Tada dolazi do još jednog prekida u njenom školovanju. Naime, ona se početkom Prvog svetskog rata ponovo prijavila da bude bolničarka, ovoga puta u Vojnoj bolnici u Kragujevcu. Studije medicine nastavila je u Monopelјeu, a diplomirala je 1919. godine u Strazburu, gde je počela da radi na Dečjoj klinici. Godine 1921. odbranila je doktorsku tezu i stekla zvanje doktora medicine.

**PORODICA**

Tokom studija, 1919. godine udala se za svog kolegu Aleksandra Kostića. Venčali su se u Monpelјeu, a crkveno venčanje obavljeno je u Nici, u ruskoj pravoslavnoj crkvi. Sa njim je imala dvoje dece, sina Ivana (Vanju) koji je 1942. godine poginuo kao borac Ravnogorskog pokreta i Vojislava (Vokija) Kostića, našeg poznatog kompozitora i gastronoma [3,6,7,8].

**POVRATAK U SRBIJU I PROFESIONALNA KARIJERA**

Po završetku studija Smilja Kostić boravila je još kratko vreme u Strasburu. Naredne, 1922. godine, vratila se sa svojim suprugom, prof. dr Aleksandrom Kostićem, u Beograd. Razlog njihovog povratka bio je primanje Aleksandra Kostića na mesto profesora histologije na novoosnovanom Medicinskom fakultetu u Beogradu. Kada je Histološki institut Medicinskog fakulteta u Beogradu dobio svoje prostorije dvadesetih godina prošlog veka, doktorka Smilja Kostić postala je prvi asistent na toj katedri.

Tu funkciju obavljala je kratko jer je naredne 1924. godine postala asistent u tek osnovanoj Dečjoj klinici, u okviru koje je ona osnovala Dečji dispanzer i potom postala šef te službe. Od tog perioda počeo je njen pionirski rad u dečjoj medicini koji je imao dalekosežne posledice. Dečji dispanzer postao je centar preventivne medicine i brige za zdravlje dece, čime je doktorka Kostić postavila temelje za modernu pedijatrijsku praksu u Srbiji.

Doktorka Smilja Kostić je primenjivala savremene svetske metode u naučnim istraživanjima, nastavi i lekarskoj praksi. Budući da je govorila nemački i francuski jezik, pored pisanja, bavila se i prevođenjem stručne literature. Objavila je preko 120 stručnih i naučnih radova i popularnih pedijatrijskih članaka na srpskom i francuskom jeziku, u domaćim i inostranim stručnim časopisima. Tokom svoje radne karijere, pored zalaganja u nastavi pedijatrije, radila je i kao glavni lekar ambulante Dečje klinike i lekar u Savetovalištu za odojčad, gde je upućivala majke u način nege i ishrane novorođenčadi. Napisala je, prve u Srbiji, priručnike za kliničku laboratorijsku dijagnostiku. Pored rada na istraživanju oboljenja srca i krvnih sudova, primene antibiotika i poremećaja metabolizma i ishrane kod dece, krajem dvadesetih godina 20. veka, njeno profesionalno interesovanje se usmerava i fokusira na veliki javnozdravstveni problem, a to je tuberkuloza kod dece, i kako sprovesti njenu preventivu.

U zvanje docenta na Katedri za pedijatriju izabrana je 1939. godine, čime je postala prva žena docent Medicinskog fakulteta. Početkom Drugog svetskog rata, 1941. godine udaljena je sa fakulteta, jer je odbila da potpiše „Apel srpskom narodu" da bi dve godine kasnije ipak bila vraćena u službu, gde je na istoj dužnosti ostala do kraja rata. Za vanrednog profesora na Katedri za pedijatriju izabrana je 1948. godine, kada je i postavljena za šefa glavnog odeljenja Dečje klinike u Beogradu [2,9,10].

Dr. Kostić's work remains highly significant today, as her discoveries and methodologies laid the foundation for further development of immunology and infectious disease medicine in Serbia and beyond. Her legacy lives on through generations of doctors and researchers who continue her mission, applying her findings and methods in the daily fight for human health. Through her dedication and passion for science, Dr. Smilja Kostić left a profound and lasting mark in medicine, and her work continues to inspire today.

## EARLY CHILDHOOD AND EDUCATION

Dr. Smilja Kostić was born as Smilja Joksić in 1895 in Belgrade, to her father Momčilo Joksić, an adjutant of the Royal Guard, and her mother Staka Pačić. She was the second of seven children born to Momčilo and Staka. She was the great-granddaughter of Toma Vučić Perišić, a participant in the First and Second Serbian Uprisings and one of the most influential figures in Serbia in the second half of the 19th century. It is assumed that she inherited from her great-grandfather her persistence, determination, and skill in dealing with people, especially children.

Her schooling was neither easy nor continuous. She completed primary and secondary education in Belgrade and passed the so-called maturity exam in 1913. During the Balkan Wars (1912–1913), at the age of seventeen, Smilja voluntarily enlisted as a nurse at the Third Reserve Hospital in Belgrade. For her great humanity and bravery shown during the Balkan Wars, she was decorated with the Cross of Mercy and the Bronze Medal of the Serbian Red Cross.

She began medical studies in 1915 in Lausanne, during the difficult years of war. Her studies were interrupted once again when, at the beginning of the First World War, she volunteered to serve as a nurse in the Military Hospital in Kragujevac. She resumed her medical studies in Montpellier and graduated in 1919 in Strasbourg, where she began working at the Children's Clinic. In 1921, she defended her doctoral thesis and earned the degree of Doctor of Medicine.

## FAMILY

During her studies, in 1919, she married her colleague Aleksandar Kostić. Their civil ceremony took place in Montpellier, and the religious wedding was held in Nice, at the Russian Orthodox Church. They had two children: a son, Ivan (Vanja), who died in 1942 as a fighter in the Ravna Gora movement, and Vojislav (Voki) Kostić, a well-known composer and gastronome. [3,6,7,8].

## RETURN TO SERBIA AND PROFESSIONAL CAREER

After completing her studies, Smilja Kostić stayed for a short time in Strasbourg. In 1922, she returned to Belgrade with her husband, Prof. Dr. Aleksandar Kostić. The reason for their return was Aleksandar Kostić's appointment as a professor of histology at the newly established Faculty of Medicine in Belgrade. When the Histological Institute of the Faculty of Medicine in Belgrade acquired its own premises in the 1920s, Dr. Smilja Kostić became the first assistant at that department.

She held this position for a short time, as in 1924 she became an assistant at the newly established Children's Clinic, where she founded the Children's Dispensary and later became head of the service. From that period, her pioneering work in pediatric medicine began, with far-reaching consequences. The Children's Dispensary became a center for preventive medicine and child health care, laying the foundation for modern pediatric practice in Serbia.

Dr. Smilja Kostić applied contemporary global methods in scientific research, teaching, and medical practice. Fluent in German and French, she not only wrote original works but also translated professional literature. She published over 120 professional and scientific papers as well as popular pediatric articles in Serbian and French, in both domestic and international journals.

During her career, in addition to her dedication to pediatric education, she worked as chief physician of the Children's Clinic outpatient department and as a physician in the Infant Advisory Clinic, where she guided mothers on newborn care and nutrition. She authored the first manuals in Serbia for clinical laboratory diagnostics. Besides research on cardiovascular diseases, antibiotic applications, and metabolic and nutritional disorders in children, by the late 1920s her professional focus shifted to a major public health problem—childhood tuberculosis—and its prevention.

She was appointed assistant professor at the Department of Pediatrics in 1939, becoming the first female assistant professor at

**DOPRINOS U PREVENTIVI TUBERKULOZE I UVOĐENjU BCG VAKCINE**

Doktorka Smilja Kostić bila je pionirka u borbi protiv tuberkuloze kod dece u Jugoslaviji. Njeno zalaganje za uvođenje preventivnih mera i primenu BCG vakcine predstavljalo je ključni korak u smanjenju stope obolevanja i smrtnosti od ove opasne bolesti.

U prvoj polovini 20. veka tuberkuloza je bila jedna od najsmrtonosnijih bolesti, posebno u siromašnim i ratom pogođenim regijama poput Jugoslavije. Deca su bila među najranjivijim grupama, često oboljevajući zbog loših uslova života, neadekvatne ishrane i nedostatka medicinske nege. U to vreme naša zemlja je imala jednu od najvećih stopa smrtosti dece uzrasta do 5 godina, obolelih od ove bolesti. Doktorka Kostić prepoznala je ozbiljnost problema i posvetila svoj rad suzbijanju tuberkuloze kroz prevenciju i edukaciju. Kao šef Dečjeg dispanzera inicirala je programe ranog otkrivanja i lečenja tuberkuloze kod dece, što je predstavljalo revolucionaran pristup u to vreme.

Jedno od njenih najvažnijih dostignuća bilo je uvođenje BCG vakcine u našu zemlju. Ova vakcina, razvijena u Francuskoj 1920-ih godina, postala je osnovni alat u borbi protiv tuberkuloze širom sveta. Međutim, njeno uvođenje u Jugoslaviju bilo je izazovno zbog nedostatka resursa, stručnog kadra i svesti o važnosti imunizacije. Doktorka Kostić se neumorno zalagala za primenu BCG vakcine, koristeći naučne dokaze i međunarodna iskustva kako bi ubedila vlasti i zdravstvo o njenoj efikasnosti. Organizovala je kampanje edukacije i podizanja svesti među lekarima i stanovništvom, što je dovelo do postepenog prihvatanja vakcinacije. Njeni napori kulminirali su početkom masovne imunizacije dece protiv tuberkuloze, što je ubrzo rezultiralo značajnim smanjenjem broja obolelih.

Doktorka Kostić nije samo uvela vakcinu, već je radila i na implementaciji sveobuhvatnih preventivnih mera. Kroz rad u Dečjem dispanzeru, razvila je programe koji su uključivali redovne zdravstvene preglede, ranu dijagnostiku i lečenje dece sa tuberkulozom ili rizikom od oboljevanja. Posebno se posvetila edukaciji majki i porodica o značaju higijene, ishrane i zdravih životnih uslova u prevenciji bolesti. Njeni programi uključivali su i obuku medicinskog osoblja, kako bi se obezbedila adekvatna briga za decu u celoj zemlji. Njeni rezultati, koji su pokazivali praktičnu vrednost i neškodljivost ove vakcine, ocenjeni su u Pasterovom institutu i dečjim klinikama u Parizu i Stokholmu kao značajan naučni doprinos.

Za svoj izuzetan doprinos u borbi protiv tuberkuloze, doktorka Smilja Kostić dobila je veoma važno priznanje. Godine 1952. odlikovana je Nacionalnim ordenom Legije časti od strane Francuske, što je bilo jedno od najprestižnijih priznanja u to vreme. Predsednik Francuske joj je uručio i broš sa brilijantima u obliku inicijala "BCG", čime je odata počast njenom pionirskom radu na promociji ove vakcine. Njen suprug, prof. dr Aleksandar Kostić, odlikovan je istim ordenom 12 godina ranije, za doprinos nauci. U trenutku njenog odlikovanja, na svetu postoji još samo jedan bračni par koji nosi ista odlikovanja. To su Marija i Pjer Kiri [2,8,11].

**PROFESIONALNI IZAZOVI**

Tokom svoje, iako uspešne karijere, suočavala se sa brojnim preprekama i poteškoćama. Na domaćem terenu se na pojedine stavove i ponašanje ove požrtvovane lekarke nije blagonaklono gledalo. Obzirom da se i u posleratnom periodu nije angažovala ni u jednoj ideološkoj organizaciji, označena je kao profesor koji ispoljava neprijateljski stav prema socijalističkoj zajednici. Njeni ideološko-politički stavovi nisu se uklapali društvo, u kome je od intelektualaca, a posebno profesora Univerziteta, tražena saradnja i lojalnost. Nakon dobro organizovane političke kampanje, zvanično je moralno-politički diskreditovana i 1. juna 1954. godine penzionisana, odnosno udaljena sa fakulteta [9,12].

**KASNIJI ŽIVOT I NASLEĐE**

Smilja i Aleksandar Kostić su od mladih godina bili nerazdvojni. Živeli su u zajedništvu 70 godina, dočekavši duboku starost. Nakon udaljavanja sa Medicinskog fakulteta, poslednje tri decenije života doktorka Smilja Kostić bila je posvećena privatnoj praksi i pomaganju suprugu u pisanju i ostvarivanju istraživačkih poduhvata. Preminula je 5. juna 1981. godine u Beogradu, u porodičnom stanu u Dositejevoj 1. Zahvaljujući njihovom sinu, Vokiju Kostiću, supružnici počivaju zajedno u Aleji zaslužnih građana na Novom groblju u Beogradu. Prema njihovoj želji na spomen-ploči ispisan je tekst: NERAZDVOJNI ZA ŽIVOTA, NERAZDVOJNI POSLE SMRTI

Smilja Kostić je, 2001. godine, moralno rehabilitovana i to kao jedina žena u grupi od

the Faculty of Medicine. At the beginning of World War II in 1941, she was removed from the faculty for refusing to sign the "Appeal to the Serbian People," but two years later she was reinstated and continued in her position until the end of the war. She was promoted to associate professor at the Department of Pediatrics in 1948, and at the same time appointed head of the main department of the Children's Clinic in Belgrade. [2,9,10].

## CONTRIBUTION TO TUBERCULOSIS PREVENTION AND INTRODUCTION OF THE BCG VACCINE

Dr. Smilja Kostić was a pioneer in the fight against childhood tuberculosis in Yugoslavia. Her dedication to implementing preventive measures and the use of the BCG vaccine represented a crucial step in reducing the incidence and mortality of this dangerous disease.

In the first half of the 20th century, tuberculosis was one of the deadliest diseases, especially in poor and war-affected regions like Yugoslavia. Children were among the most vulnerable groups, often falling ill due to poor living conditions, inadequate nutrition, and lack of medical care. At that time, the country had one of the highest child mortality rates under the age of five caused by tuberculosis. Dr. Kostić recognized the seriousness of the problem and dedicated her work to combating tuberculosis through prevention and education. As the head of the Children's Dispensary, she initiated programs for early detection and treatment of tuberculosis in children, a revolutionary approach at the time.

One of her most important achievements was the introduction of the BCG vaccine in Yugoslavia. This vaccine, developed in France in the 1920s, became a fundamental tool in the global fight against tuberculosis. Its introduction in Yugoslavia faced challenges due to lack of resources, trained personnel, and awareness of the importance of immunization. Dr. Kostić tirelessly advocated for the vaccine, using scientific evidence and international experience to convince authorities and the health system of its effectiveness. She organized educational campaigns to raise awareness among doctors and the general population, which led to the gradual acceptance of vaccination. Her efforts culminated in the beginning of mass immunization of children against tuberculosis, which soon resulted in a significant reduction in the number of cases.

Dr. Kostić not only introduced the vaccine but also worked on implementing comprehensive preventive measures. Through her work at the Children's Dispensary, she developed programs including regular health check-ups, early diagnosis, and treatment for children with tuberculosis or at risk of infection. She focused particularly on educating mothers and families about the importance of hygiene, nutrition, and healthy living conditions in disease prevention. Her programs also included training of medical personnel to ensure proper care for children nationwide. Her results, demonstrating the practical value and safety of the vaccine, were recognized by the Pasteur Institute and children's clinics in Paris and Stockholm as a significant scientific contribution.

For her exceptional contribution to the fight against tuberculosis, Dr. Smilja Kostić received a highly prestigious award. In 1952, she was decorated with the National Order of the Legion of Honor by France, one of the most esteemed recognitions at the time. The French President also presented her with a brooch in the shape of the initials "BCG" set with diamonds, honoring her pioneering work in promoting the vaccine. Her husband, Prof. Dr. Aleksandar Kostić, had received the same award 12 years earlier for his contributions to science. At the time of her decoration, there was only one other couple in the world with the same distinction: Marie and Pierre Curie [2,8,11].

## PROFESSIONAL CHALLENGES

During her successful career, she faced numerous obstacles and difficulties. In her home country, some of her attitudes and actions were not well regarded. Because she did not participate in any ideological organization in the post-war period, she was labeled as a professor showing a hostile stance toward the socialist community. Her ideological and political positions did not align with the society's expectations, where intellectuals, particularly university professors, were required to show cooperation and loyalty. After a well-organized political campaign, she was officially morally and politically discredited and retired on June 1, 1954, effectively being removed from the faculty [9,12].

ukupno trideset i jednog profesora koji su posle rata bili uklonjeni sa fakulteta. Godine 2018. u okviru obnovljene prostorne kulturno-istorijske celine – Gročanska čaršija, od velikog značaja za Republiku Srbiju, u izložbenoj galeriji u Biblioteci „Ilija Garašanin", predstavljen je javnosti Legat prof. dr Aleksandra Kostića opštine Grocka, gde je, baš kao i u životu, svoje mesto uz supruga našla i Smilja [2].

## ZAKLJUČAK

Život i rad doktorke Smilje Kostić predstavljaju primer nepokolebljive posvećenosti nauci, medicini i humanosti. Kao prva žena docent na Medicinskom fakultetu Univerziteta u Beogradu, doktorka Kostić probijala je granice u vreme kada je uloga žena u nauci bila ograničena. Njena pionirska dostignuća u oblasti pedijatrije i javnog zdravlja ostavila su neizbrisiv trag u medicinskoj istoriji naše zemlje. Doktorka Kostić nije samo lečila, već je i obrazovala i inspirisala svoje studente, kolege i zajednicu da prepoznaju značaj zdravlja i prevencije.

Iako je njen rad bio priznat širom sveta, suočavala se sa brojnim izazovima. Njen nesebični rad i istrajnost nisu uvek bili cenjeni u političkom i društvenom kontekstu njenog vremena, što je rezultiralo nepravdom kada je uklonjena sa Medicinskog fakulteta. Međutim, njena posthumna rehabilitacija i priznanje doprinosa samo potvrđuju da se pravi značaj njenog rada ne može zanemariti. Dr Smilja Kostić bila je mnogo više od lekara i naučnika. Bila je humanista, lider i vizionar, čiji je uticaj nadmašio granice medicine. Njena zaostavština živi kroz zdravlje generacija dece, unapređene javnozdravstvene sisteme i inspiraciju koju pruža novim generacijama lekara. Kroz posvećenost i upornost, postala je simbol borbe za nauku, pravdu i bolji život za sve. Njeno ime ostaje zapisano u istoriji kao sinonim za integritet, stručnost i ljubav prema čoveku.

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## LATER LIFE AND LEGACY

Smilja and Aleksandar Kostić were inseparable from their youth. They lived together for 70 years, reaching old age side by side. After being removed from the Faculty of Medicine, Dr. Smilja Kostić dedicated the last three decades of her life to private practice and assisted her husband in writing and research endeavors. She passed away on June 5, 1981, in Belgrade, in the family apartment at Dositejeva 1. Thanks to their son, Vokie Kostić, the couple rests together in the Alley of Distinguished Citizens at the New Cemetery in Belgrade. According to their wish, the memorial plaque reads:

"INSEPARABLE IN LIFE, INSEPARABLE AFTER DEATH."

Dr. Smilja Kostić was morally rehabilitated in 2001, becoming the only woman among 31 professors removed from the faculty after the war to receive this recognition. In 2018, as part of the renovated Grocka cultural-historical complex, her legacy was publicly showcased in the exhibition gallery of the Ilija Garašanin Library, where, alongside her husband, she found her place in life and posthumously [2].

## CONCLUSION

The life and work of Dr. Smilja Kostić exemplify unwavering dedication to science, medicine, and humanity. As the first female assistant professor at the Faculty of Medicine, University of Belgrade, she broke barriers at a time when women's roles in science were limited. Her pioneering achievements in pediatrics and public health left an indelible mark on the medical history of Serbia.

Dr. Kostić not only treated patients, but also educated and inspired her students, colleagues, and community to recognize the importance of health and prevention. Although her work was internationally recognized, she faced many challenges. Her selfless dedication and perseverance were not always appreciated in the political and social context of her time, resulting in the injustice of her removal from the Faculty of Medicine.

Her posthumous rehabilitation and recognition confirm the lasting significance of her work. Dr. Smilja Kostić was more than a doctor and scientist; she was a humanist, leader, and visionary, whose impact transcended medicine. Her legacy lives on through the health of generations of children, improved public health systems, and the inspiration she provides to new generations of physicians. Through her commitment and persistence, she became a symbol of the fight for science, justice, and a better life for all. Her name remains recorded in history as a synonym for integrity, expertise, and love for humanity..

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# UKRAŠAVANJE ZUBA KROZ ISTORIJU: IZMEĐU ESTETIKE, IDENTITETA I RITUALA

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**Sažetak:** Ukrašavanje zuba je praksa prisutna u brojnim civilizacijama širom sveta, koja često prevazilazi čistu estetiku i ulazi u sferu identiteta, rituala i duhovnosti. Od umetanja dragog kamenja kod Maja, preko crnjenja zuba u Japanu, do savremenih trendova poput grillz-a, dentalna ornamentacija svedoči o raznolikosti ljudskih kulturnih izraza. Ovaj rad istražuje istorijski razvoj ukrašavanja zuba, njegovu simboliku i značaj kroz vekove, uz razmatranje uticaja na savremenu stomatološku praksu.
**Ključne reči**: ukrašavanje zuba, dentalna ornamentika, kulturne prakse, simbolika, istorija stomatologije, ritualna modifikacija zuba, estetska stomatologija

## UVOD

Modifikacija tela u estetske, socijalne i religiozne svrhe stara je koliko i sama civilizacija [1]. U gotovo svim delovima sveta, ljudska potreba za izražavanjem identiteta, pripadnosti ili statusa reflektovala se kroz intervencije na telu, uključujući i one na zubima [2]. Zubi, kao izloženi i lako uočljivi deo lica, igrali su ključnu ulogu u mnogim ritualnim i dekorativnim praksama. Njihova transformacija – bilo kroz pigmentaciju, umetanja plemenitih metala i dragog kamenja, brušenje u različite oblike, ili čak namerno vađenje. Takve prakse nalazimo među civilizacijama Mezoamerike, naročito Majama, zatim u staroegipatskim grobnicama, kao i širom istočne i jugoistočne Azije – u Japanu, Kini i na Filipinima [3,4]. Svaka od ovih kultura razvila je jedinstvene tehnike i estetske norme koje su odražavale njihove kosmologije, društvene hijerarhije i ideje o lepoti [5].

U ovom radu fokusiramo se na geografski i hronološki raznolike primere ukrašavanja zuba kroz istoriju, sa ciljem da se identifikuju i analiziraju kulturna značenja, tehnike i materijali koji su korišćeni.

## DREVNE CIVILIZACIJE

Jedan od najupečatljivijih oblika dentalne modifikacije u drevnoj mezoameričkoj civilizaciji jeste praksa ukrašavanja zuba među Majama. Ova praksa je imala višestruku simboliku i bila je usko povezana sa estetikom, socijalnim statusom i religijskim verovanjima. Maje su najčešće bušile male otvore u prednjim zubima pomoću rotacionih alata, u koje su umetali poludrago kamenje poput žada, tirkiza ili hematita. Umetanje žada, koji je u njihovoj kulturi simbolisao besmrtnost, moć i povezanost s božanstvima, posebno je bilo rezervisano za pripadnike elite [6].

Pored ugradnje kamenja, uobičajena je bila i praksa modifikacije oblika zuba kroz brušenje, kojom su se formirali špicasti, T-oblikovani ili urezani zubi. Ovi zahvati su se izvodili u mladosti, verovatno u okviru rituala inicijacije, čime su dodatno dobijali na socijalnom i duhovnom značaju. Neke zajednice su čak praktikovale bojenje ili crnjenje zuba specijalnim supstancama, što se smatralo znakom čistoće i privlačnosti. Ove sofisticirane intervencije ukazuju na visok stepen tehničke veštine drevnih Maja, kao i na duboku ukorenjenost oralne estetike u njihovoj kulturi i svakodnevnom životu [7].

Kod naroda Anda, poput Inka, zabeleženi su slučajevi simboličkog brušenja zuba, ali i korišćenja pigmenata za bojenje u crveno ili crno. Verovalo se da određene boje štite od zlih duhova ili pomažu pri ritualnim transformacijama. Iako nisu umetali ukrase kao Maje, značaj zuba bio je prisutan u mnogim ceremonijama.

Za razliku od Maja, kod drevnih Egipćana nema direktnih dokaza o ugradnji dragog kamenja u zube, niti o svesnoj modifikaciji oblika zuba u dekorativne svrhe. Međutim, određeni nalazi ukazuju na to da su Egipćani pridavali veliku pažnju oralnoj higijeni i estetici. Takođe su razvili rane oblike stomatoloških zahvata, uključujući povezivanje rasklaćenih zuba zlatnim žicama, što neki tumače kao rani oblik stomatološke protetike. U


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# TOOTH DECORATION THROUGH HISTORY: BETWEEN AESTHETICS, IDENTITY, AND RITUAL

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**Abstract:** Tooth decoration has been practiced by various civilizations worldwide, often extending beyond aesthetics into the realms of identity, ritual, and spirituality. From gemstone inlays among the Maya, to tooth blackening in Japan, and contemporary trends such as grillz, dental ornamentation represents a rich spectrum of cultural expression. This paper examines the historical development, symbolic meanings, and cultural significance of tooth decoration, with particular attention to its implications for modern dental practice

**Keywords:** tooth decoration, dental ornamentation, cultural practices, symbolism, history of dentistry, ritual tooth modification, aesthetic dentistry

## INTRODUCTION

Body modification for aesthetic, social, and religious purposes is as old as civilization itself [1]. In nearly all parts of the world, the human need to express identity, affiliation, or status has been reflected through bodily interventions, including those involving teeth [2]. Teeth, as prominent and easily visible facial elements, have played a key role in many ritualistic and decorative practices. Their transformation—whether through pigmentation, the insertion of precious metals and gemstones, filing into various shapes, or even deliberate extraction—has been observed across different cultures. Such practices can be found among the civilizations of Mesoamerica, especially the Maya, in ancient Egyptian tombs, and throughout East and Southeast Asia—in Japan, China, and the Philippines [3,4]. Each of these cultures developed unique techniques and aesthetic norms that reflected their cosmologies, social hierarchies, and concepts of beauty [5].

This paper focuses on geographically and chronologically diverse examples of dental adornment throughout history, aiming to identify and analyze the cultural meanings, techniques, and materials used in these practices.

## ANCIENT CIVILIZATIONS

One of the most striking forms of dental modification in ancient Mesoamerican civilization was the practice of tooth decoration among the Maya. This practice carried deep symbolic meanings and was closely tied to aesthetics, social status, and religious beliefs. The Maya often drilled small holes into their front teeth using rotary tools, into which they embedded semi-precious stones such as jade, turquoise, or hematite. Jade, symbolizing immortality, power, and a connection with deities, was especially reserved for members of the elite [6].

In addition to gemstone inlays, tooth reshaping through filing was also common, producing pointed, T-shaped, or notched forms. These procedures were typically performed during youth, likely as part of initiation rites, adding to their social and spiritual significance. Some communities even practiced staining or blackening of the teeth with special substances, which was considered a sign of purity and attractiveness. These sophisticated interventions demonstrate the high level of technical skill possessed by the ancient Maya, as well as the deeply rooted importance of oral aesthetics in their culture and daily life [7].

Among Andean peoples such as the Inca, symbolic tooth filing and the use of red or black pigments were practiced. Certain colors were believed to offer protection from evil spirits or aid in ritual transformation. Although the Incas did not embed decorations as the Maya did, the symbolic importance of teeth was evident in many ceremonial contexts.

In contrast to the Maya, there is no direct evidence of gemstone inlays or deliberate aesthetic reshaping of teeth among the ancient Egyptians. However, archaeological findings

grobnicama bogatih pojedinaca pronađene su proteze i umetci od zlata, koji su najverovatnije imali i estetsku i simboličku funkciju, kao i dokaz statusne pripadnosti. U nekim slučajevima, zubi su bili povezivani zlatnim žicama, verovatno nakon smrti, u okviru pogrebnih priprema koje su imale za cilj očuvanje "celovitosti tela" za zagrobni život [8].

**KINA I ISTOČNA AZIJA**

U istočnoazijskim kulturama, dominantne prakse odnosile su se na bojenje, crnjenje i površinsku modifikaciju. U staroj Kini, naročito tokom dinastija Han i Tang, praksa bojenja zuba bila je prisutna u ruralnim oblastima i naročito među etničkim manjinama. Crnjenje zuba imalo je višestruku simboliku – od zaštite od zlih duhova, preko izraza čistoće, do vizuelnog izraza harmonije, u skladu s taoističkim principima jina i janga [9].

Ovakva praksa kasnije je primenjivana i u Vijetnamu. Najpoznatija praksa u Japanu bila je ohaguro, estetski ritual crnjenja zuba koji se praktikovao od Heian perioda (9. vek) do kraja 19. veka. Ohaguro je bio znak zrelosti, ženstvenosti, vernosti i sofisticiranosti, a u nekim periodima i deo samurajske kulture. Proces je uključivao korišćenje mešavine gvožđa, sirćeta i biljnih tpigmenata [10,11].

Za razliku od svojih azijskih suseda, drevne civilizacije na Filipinima, razvile su izuzetno kompleksne oblike ukrašavanja zuba zlatnim nadoknadama. Arheološki nalazi, poput poznate Bolinao lobanje, pokazuju da su pojedinci u predkolonijalnom periodu imali umetke od zlata i gravure na prednjim zubima – što je predstavljalo statusni simbol i duhovnu zaštitu [12,13]. Neki vladari i plemići imali su čak i dijamantne nadoknade, što ukazuje na izuzetno razvijenu dentalnu tehniku i estetske standarde u pretkolonijalnim društvima [14].

U vedskom periodu Indije, higijena zuba imala je važnu ulogu u duhovnim i zdravstvenim praksama. Iako direktne modifikacije zuba nisu bile česte, postoje zapisi o upotrebi ajurverdskih preparata za izbjeljivanje i jačanje zuba, što je povezano s idejom duhovne i fizičke čistoće. Kasnije, među nekim aristokratskim slojevima, beleži se korišćenje umetaka i ukrasnih elemenata od zlata [15].

**AFRIKA**

Afrika je kontinent sa najraznovrsnijim i najdugovečnijim tradicijama modifikacije tela, a ukrašavanje i oblikovanje zuba imalo je važnu ulogu u mnogim zajednicama. Najčešće intervencije na zubima odnosile su se na namerno vađenje, brušenje i oštrenje i pigmentisanje zuba [16].

Narod Mangbetu (Demokratska republika Kongo) poznat je po elongaciji lobanje, ali takođe i po estetskom oblikovanju zuba. Mladim devojkama i mladićima oštrili su se prednji zubi u oblik trougla, što je predstavljalo ideal lepote i prepoznatljivost pripadnosti grupi. Ove modifikacije bile su deo inicijacijskog rituala i predstavljale su fizičku spremnost i estetsku zrelost [17].

Kod Yaka i Teke naroda (Kongo i Angola), kao i Makonde (Mozambik), brušenje zuba u šiljke bilo je ritualni čin seksualne zrelosti, ali i sredstvo za zastrašivanje neprijatelja u ratnim vremenima. Zubi su smatrani "oknima duše", pa su njihova transformacija i zaštita imali i spiritualnu dimenziju. Ovaj proces je bio bolan i često izvođen u adolescenciji [18].

Praksa bojenja zuba i tetoviranja usana crnim pigmentima među Fulani ženama u severnom Maliju i Nigeru duboko je ukorenjena u njihovoj kulturi i estetici. Ova tradicija, poznata kao *Tchoodi* ili *tunpungalle*, obuhvata tetoviranje desni, usana i brade prirodnim pigmentima, često dobijenim iz biljnih izvora poput pepela i biljnih smola. Cilj ovih modifikacija je naglašavanje bele boje zuba, što se smatra simbolom čistoće, lepote i duhovne ravnoteže. Ove prakse često se izvode tokom svečanosti i venčanja, predstavljajući obred prelaska u odraslo doba i simbolizujući hrabrost i pripadnost zajednici [19].

Pripadnici Beti i Fang naroda (Kamerun i Gabon) praktikovali su vađenje prednjih zuba iz gornje vilice kao deo inicijacije u odraslo doba. Verovalo se da taj čin oslobađa osobu od detinjstva i otvara duhovni kanal za komunikaciju sa precima. Odsustvo zuba nije se smatralo hendikepom, već znakom časti i hrabrosti [20].

U plemenima Istočne Afrike, kao što su Dinka i Nuer u Sudanu, vađenje donjih sekutića je praksa prisutna vekovima. Smatralo se da uklanjanje ovih zuba omogućava lakše unošenje hrane i lekova u slučaju bolesti, ali je isto tako bilo simboličko – označavalo je prelazak iz detinjstva u odraslo doba [21].

Iako poznati po drugim oblicima telesne modifikacije (npr. istezanje ušiju), neki Masai

indicate that Egyptians placed great emphasis on oral hygiene and aesthetics. They also developed early forms of dental procedures, including the stabilization of loose teeth with gold wire, which some interpret as an early form of dental prosthetics. In the tombs of wealthy individuals, gold prostheses and inlays have been found, likely serving both aesthetic and symbolic purposes, as well as indicating social status. In some cases, teeth were wired together post-mortem as part of funerary preparations aimed at preserving bodily "wholeness" for the afterlife [8].

**CHINA AND EAST ASIA**

In East Asian cultures, dominant dental practices involved staining, blackening, and surface modification. In ancient China, particularly during the Han and Tang dynasties, tooth coloring was practiced in rural areas and especially among ethnic minorities. Blackening of teeth carried multiple meanings—from protection against evil spirits, to expressions of purity, and visual harmony aligned with Taoist principles of yin and yang [9].

This practice later spread to Vietnam. The most notable example in Japan was ohaguro, an aesthetic ritual of tooth blackening practiced from the Heian period (9th century) until the late 19th century. Ohaguro symbolized maturity, femininity, fidelity, and sophistication, and at times was also a component of samurai culture. The process involved a mixture of iron filings, vinegar, and plant-based pigments [10,11].

Unlike their Asian neighbors, ancient Filipino civilizations developed highly complex forms of dental ornamentation using gold restorations. Archaeological discoveries such as the famous Bolinao skull reveal that individuals during the precolonial era had gold inlays and engravings on their front teeth—serving both as status symbols and spiritual protection [12,13]. Some rulers and nobles even had diamond-encrusted restorations, highlighting an advanced level of dental technology and aesthetic standards in precolonial societies [14].

During the Vedic period in India, dental hygiene played a significant role in spiritual and health practices. While direct modifications of the teeth were uncommon, records exist of Ayurvedic preparations used for whitening and strengthening teeth, associated with the concept of spiritual and physical purity. Later, among some aristocratic classes, the use of gold inlays and ornamental dental elements was also documented [15].

**AFRICA**

Africa is a continent with some of the most diverse and enduring traditions of body modification, where dental decoration and reshaping have played an important role in many communities. The most common dental interventions involved deliberate tooth extraction, filing, sharpening, and pigmentation [16].

The Mangbetu people (Democratic Republic of Congo) are known for skull elongation, but also for the aesthetic shaping of teeth. Young girls and boys would have their front teeth sharpened into a triangular shape, which represented an ideal of beauty and group identity. These modifications were part of initiation rituals and symbolized physical readiness and aesthetic maturity [17].

Among the Yaka and Teke peoples (Congo and Angola), as well as the Makonde (Mozambique), tooth filing into sharp points was a ritual act of sexual maturity and also served as a means of intimidating enemies during times of war. Teeth were considered "windows to the soul," and their transformation and protection had a spiritual dimension. This process was painful and often performed during adolescence [18].

The practice of coloring teeth and tattooing the lips with black pigments among Fulani women in northern Mali and Niger is deeply rooted in their culture and aesthetics. This tradition, known as Tchoodi or tunpungalle, includes tattooing the gums, lips, and chin with natural pigments, often derived from plant sources such as ash and resins. The goal of these modifications is to highlight the whiteness of the teeth, which is seen as a symbol of purity, beauty, and spiritual balance. These practices are often performed during ceremonies and weddings, representing a rite of passage into adulthood and symbolizing courage and community belonging [19].

Members of the Beti and Fang peoples (Cameroon and Gabon) practiced the removal of upper front teeth as part of initiation into adulthood. It was believed that this act liberated the individual from childhood and opened a spiritual channel for communication with ancestors. The absence of teeth was not seen as a handicap, but as a sign of honor and bravery [20].

ratnici (Kenija i Tanzanija) su tokom inicijacije vadili zube kao simbol žrtve i muškosti. Takođe su praktikovali oblike tradicionalne dentalne terapije, što je često uključivalo simboličko „lečenje“ bola pigmentacijom i ritualima [22].

**EVROPA**

Ukrašavanje zuba u Evropi ima specifičan razvojni put, različit od tradicija drugih kontinenata, i uglavnom je bio usko povezan sa društvenim statusom, estetikom i tehnološkim mogućnostima epohe.

Postoje arheološki nalazi koji ukazuju na to da su još u antičkom Rimu bogatiji slojevi koristili zubne umetke izrađene od zlata ili kostiju. Iako su funkcionalnost i restauracija bili u fokusu, postojali su i estetski elementi ukrašavanja [23]. Briga o belini zuba i oralnoj higijeni bila je deo kulturnih normi, a očuvani osmesi smatrani su znakom uglađenosti.

Tokom srednjeg veka, dominacija hrišćanske dogme je umanjila značaj telesne estetike, ali su među evropskim plemstvom Italije i Francuske zlatni i srebrni zubi bili statusni simboli. Ove modifikacije nisu imale zdravstvenu funkciju, već su bile deo dvorskog luksuza i lične estetike [24]. Paralelno, u ruralnim oblastima Evrope, poput Škotske i Irske, bojenje zuba biljnim pigmentima, naročito korišćenjem kore drveta, bilo je rasprostranjeno među ženama. Tamniji zubi smatrani su znakom skromnosti i pobožnosti.

Za periodu od XVII do XIX veka vezuje se revolucija u stomatološkoj protetici. U Engleskoj i Francuskoj razvijena je sofisticirana stomatološka protetika, a estetika belog osmeha postaje dominantni ideal povezan sa čistoćom i moralnošću. U ovom periodu poznat je fenomen "Waterloo teeth" – prirodni zubi uzimani sa bojnog polja nakon bitke kod Waterlooa i korišćeni za izradu proteza za bogatije slojeve [25].

Tokom perioda španske inkvizicije (1478–1834), Katolička crkva je strogo zabranjivala "neprirodno ukrašavanje" tela, uključujući i zube, smatrajući takve prakse jeretičkim i suprotnim verskim normama. Iako ne postoje konkretni dokazi o gravurama na zubima kao tajnim verskim simbolima, poznato je da su neki tajni verski redovi koristili diskretne oznake na telu kao znak pripadnosti i duhovne posvećenosti [26].

U slovenskim narodima, naročito u Ukrajini i Rusiji, arheološki nalazi svedoče o praksama ukrašavanja zuba metalnim žicama i zlatnim nitima, često u ceremonialne svrhe. Ratnici su nosili umetke kao znak hrabrosti i plemenske pripadnosti, dok su aristokrati razvijali rane oblike dentalnih nadoknada koristeći zlato i sedef [27].

**SAVREMENE SUBKULTURE I UMETNIČKA PRAKSA**

Savremene tehnologije omogućile su da ukrašavanje zuba postane manje invazivno, pristupačnije i bezbednije za pacijente. U 20. i 21. veku, evropske umetničke i muzičke subkulture (npr. punk, goth i hip-hop zajednice) popularizuju ukrašavanje zuba kroz pirsinge, ukrasne navlake za zube (grillz – eng.) i laserske gravure. U Nemačkoj i Francuskoj pojavljuju se i umetnici koji graviraju slike i poruke na dentalne fasete, kombinujući stomatologiju i umetnost [28].

Zubni kristali, poznati kao *tooth gems*, ostaju među najpopularnijim estetskim dodacima. Noviji trend naglašava minimalizam – koriste se sitni cirkoni, dijamanti ili oblici poput zvezda, meseca i sličnih simbola [29]. Pojava nano-tetovaža za zube donosi novinu u estetskoj stomatologiji. Ove privremene tetovaže nanose se direktno na gleđ i traju od nekoliko dana do jedne nedelje. Bezbedne su za upotrebu i često se koriste za specijalne prilike [30].

U urbanim stilovima raste popularnost zlatnih i metalnih navlaka koje pokrivaju samo jedan zub – najčešće očnjak ili lateralni sekutić. Savremene verzije ovih ukrasa su sofisticirane, često sa mat završnicom ili u boji roze zlata.

Zubni ukrasi koji svetle pod UV svetlom postali su trend među posetiocima festivala i noćnih događaja. Ovi ukrasi se lako postavljaju i uklanjaju, ne oštećuju zube i dostupni su u različitim bojama i oblicima [31].

Iako su *grillz* odavno prisutni u popularnoj kulturi, savremeni primerci su znatno sofisticiraniji – izrađuju se uz pomoć intraoralnog skeniranja i 3D dizajna, često sadrže gravure, simbole ili inicijale, a izrađuju se od različitih legura metala [32].

Jedan od najsavremenijih izraza u domenu zubne estetike predstavlja koncept geometrijskih porcelanskih faseta - *lovja*. Ove fasete, poznate po specifičnom površinskom reljefu sa višestranim geometrijskim oblicima (*dentagoni*), izrađuju se od visokoestetske keramike i odlikuju se preciznošću i individualnim dizajnom [33].

In East African tribes such as the Dinka and Nuer in Sudan, the removal of lower incisors has been practiced for centuries. It was believed that extracting these teeth made it easier to ingest food and medicine during illness, but it also had symbolic meaning—it marked the transition from childhood to adulthood [21].

Although more widely known for other forms of body modification (e.g., ear stretching), some Maasai warriors (Kenya and Tanzania) had their teeth removed during initiation as a symbol of sacrifice and masculinity. They also practiced forms of traditional dental therapy, often involving symbolic "treatment" of pain through pigmentation and rituals [22].

**EUROPE**

Dental decoration in Europe followed a distinct developmental path, differing from the traditions of other continents, and was mostly closely associated with social status, aesthetics, and the technological capabilities of the time.

Archaeological findings suggest that as early as ancient Rome, wealthier classes used dental inlays made of gold or bone. While the focus was on functionality and restoration, there were also aesthetic elements of adornment [23]. Concern for white teeth and oral hygiene was part of cultural norms, and well-preserved smiles were seen as a sign of refinement.

During the Middle Ages, the dominance of Christian dogma diminished the importance of bodily aesthetics, but among the European nobility in Italy and France, gold and silver teeth were status symbols. These modifications had no health-related purpose and were part of courtly luxury and personal aesthetics [24]. Simultaneously, in rural areas of Europe, such as Scotland and Ireland, coloring teeth with plant-based pigments—especially using tree bark—was common among women. Darker teeth were seen as a sign of modesty and piety.

The period from the 17th to the 19th century marked a revolution in dental prosthetics. In England and France, sophisticated prosthodontics were developed, and the aesthetic of a white smile became a dominant ideal linked to cleanliness and morality. This period is known for the phenomenon of "Waterloo teeth"—natural teeth collected from the battlefield after the Battle of Waterloo and used to make dentures for the wealthy [25].

During the Spanish Inquisition (1478–1834), the Catholic Church strictly forbade "unnatural adornment" of the body, including the teeth, deeming such practices heretical and contrary to religious norms. Although there is no concrete evidence of engravings on teeth as secret religious symbols, it is known that some clandestine religious orders used discreet body markings as signs of affiliation and spiritual devotion [26].

Among Slavic peoples, particularly in Ukraine and Russia, archaeological findings show practices of decorating teeth with metal wires and gold threads, often for ceremonial purposes. Warriors wore inlays as signs of courage and tribal affiliation, while aristocrats developed early forms of dental prosthetics using gold and mother-of-pearl [27].

**CONTEMPORARY SUBCULTURES AND ARTISTIC PRACTICE**

Modern technologies have made dental decoration less invasive, more accessible, and safer for patients. In the 20th and 21st centuries, European artistic and musical subcultures (e.g., punk, goth, and hip-hop communities) popularized dental adornment through piercings, decorative tooth covers (grillz), and laser engravings. In Germany and France, artists have emerged who engrave images and messages onto dental veneers, merging dentistry with art [28].

Tooth gems remain among the most popular aesthetic dental accessories. A recent trend emphasizes minimalism—tiny zirconia stones, diamonds, or shapes such as stars, moons, and similar symbols are commonly used [29]. The emergence of nano-tattoos for teeth introduces a novelty in aesthetic dentistry. These temporary tattoos are applied directly to the enamel and last from several days to a week. They are safe for use and often chosen for special occasions [30].

In urban styles, there is growing popularity of gold and metallic caps that cover a single tooth—most often a canine or lateral incisor. Contemporary versions of these accessories are sophisticated, often featuring matte finishes or rose gold coloring.

Tooth decorations that glow under UV light have become a trend among festivalgoers and attendees of nighttime events. These adornments are easy to apply and remove, do not damage the teeth, and come in various colors and shapes [31].

Although grillz have long been present in popular culture, modern examples are far

## ZAKLJUČAK

Ukrašavanje zuba kroz istoriju odražava složenu povezanost između estetike, identiteta i rituala. Od drevnih civilizacija, gde su zubi služili kao simbol statusa i religijskih verovanja, do savremenih trendova koji povezuju lično izražavanje sa tehnologijom, ovaj fenomen je evoluirao kroz vreme. Danas, uz pomoć novih stomatoloških tehnologija, ukrašavanje zuba postaje pristupačnije i manje invazivno, omogućavajući veću personalizaciju. Iako su se simbolički i društveni aspekti menjali, ukrašavanje zuba ostaje važan oblik identifikacije, sa potencijalom da se u budućnosti razvija i dalje, u skladu sa potrebama savremenog društva.

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more advanced—they are crafted using intraoral scanning and 3D design, often incorporating engravings, symbols, or initials, and are made from various metal alloys [32].

One of the most modern expressions in the field of dental aesthetics is the concept of geometric porcelain veneers—lovja. These veneers, known for their unique surface texture featuring multifaceted geometric shapes (dentagons), are made from highly aesthetic ceramics and are characterized by precision and individualized design [33].

## CONCLUSION

Dental decoration throughout history reflects a complex connection between aesthetics, identity, and ritual. From ancient civilizations, where teeth symbolized status and religious beliefs, to modern trends that merge personal expression with technology, this phenomenon has evolved over time. Today, thanks to new dental technologies, tooth decoration is becoming more accessible and less invasive, allowing for greater personalization. Although the symbolic and social aspects have changed, dental decoration remains an important form of identification, with the potential to further evolve in response to the needs of contemporary society.

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# EPIGENETSKE TEORIJE BRUSA LIPTONA I NJIHOVA NAUČNA EVALUACIJA

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**Sažetak:** Rad analizira epigenetske teorije Brusa Liptona i njihovu naučnu evaluaciju. Lipton, bivši profesor ćelijske biologije, osporava tradicionalni genetski determinizam tvrdeći da uverenja i percepcije mogu direktno uticati na ekspresiju gena. U svojoj knjizi "Biologija verovanja" ističe da ćelijska membrana, a ne DNK, funkcioniše kao "mozak" ćelije koji posreduje između okruženja i genetske ekspresije. Naučna zajednica priznaje neke osnovne uvide o epigenetici, ali izražava značajne rezerve prema Liptonovim tvrdnjama o direktnom uticaju misli na DNK, naglašavajući metodološke nedostatke i problematičnu primenu kvantne fizike na biološke sisteme. Uprkos kritikama, njegove teorije otvaraju važna pitanja o interakciji uma i tela, sa potencijalnim implikacijama za razvoj integrativne medicine. Najznačajniji Liptonov doprinos leži u izazivanju postojećih paradigmi i podsticanju dijaloga između različitih pristupa zdravlju koji prevazilaze strogo mehanicistički model ljudskog tela.
**Ključne reči:** epigenetika, Brus Lipton, biologija verovanja, ćelijska membrana

## UVOD

U proteklim decenijama, naučno razumevanje genetike značajno se promenilo, što je dovelo do preispitivanja tradicionalnih shvatanja molekularne biologije. Epigenetika, koja proučava promene u ekspresiji gena bez izmene DNK sekvence, otvorila je nove teorije o interakciji organizama sa okruženjem. U tom kontekstu, rad Brusa Liptona se izdvaja kao jedan od najuticajnijih, ali i kontroverznih doprinosa savremenom razumevanju genetskog determinizma. Kao bivši profesor ćelijske biologije, Lipton dovodi u pitanje dominantni dogmat molekularne biologije, koji tvrdi da genetski materijal isključivo određuje strukturu i funkciju živih bića. On predlaže model u kojem ćelijska membrana igra ključnu ulogu u interakciji između organizma i okruženja, sugerišući da naša uverenja i percepcije mogu direktno uticati na biohemijske procese i ekspresiju gena. Ovaj rad analizira Liptonove teorije, kritički ih sagledava i istražuje njihove implikacije za budućnost medicine, uz naglasak na tenziji između mehanicističkog i holističkog pristupa zdravlju i bolesti.

## REVOLUCIJA U RAZUMEVANJU GENA: LIPTONOV EPIGENETSKI PREOKRET

Brus Lipton (eng. *Bruce Lipton*) je biolog i autor koji je poznat po svojim kontroverznim idejama o epigenetici i svesti. Njegove knjige, kao što je "Biologija verovanja", istražuju vezu između misli i bioloških procesa. Lipton tvrdi da naša uverenja i percepcije mogu uticati na naše gene i ćelijsku biologiju, što je ideja koja odstupa od tradicionalne molekularne biologije. Pre svoje karijere pisca, radio je kao profesor ćelijske biologije na medicinskom fakultetu. Njegov lik je prikazan na narednoj slici.

**Slika 1.** Brus Lipton, molekularni biology
Izvor: https://www.edurazvoj.com/da-li-geni-odredjuju-sudbinu-deteta-ili-je-za-to-odgovorna-okolina-epigenetika-daje-odgovor/

Tokom proteklih decenija, razumevanje genetike je doživelo značajne promene koje su dovele do preispitivanja tradicionalnih paradigmi molekularne biologije. U tom kontekstu, rad Brusa Liptona predstavlja jedan od najkontroverznijih doprinosa savremenom


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# EPIGENETIC THEORIES OF BRUCE LIPTON AND THEIR SCIENTIFIC EVALUATION

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**Summary:**The paper analyzes Bruce Lipton's epigenetic theories and their scientific evaluation. Lipton, a former professor of cellular biology, challenges traditional genetic determinism by claiming that beliefs and perceptions can directly influence gene expression. In his book The Biology of Belief, he emphasizes that the cell membrane, rather than DNA, functions as the "brain" of the cell, mediating between the environment and genetic expression. While the scientific community acknowledges some fundamental insights in epigenetics, it expresses significant reservations about Lipton's claims regarding the direct impact of thoughts on DNA, highlighting methodological shortcomings and the problematic application of quantum physics to biological systems. Despite the criticisms, his theories raise important questions about mind–body interactions, with potential implications for the development of integrative medicine. Lipton's most notable contribution lies in challenging existing paradigms and fostering dialogue between different approaches to health that go beyond the strictly mechanistic model of the human body.
**Key words:** epigenetics, Bruce Lipton, biology of belief, cell membrane

## INTRODUCTION

In recent decades, scientific understanding of genetics has changed significantly, leading to a reevaluation of traditional concepts in molecular biology. Epigenetics, which studies changes in gene expression without altering the DNA sequence, has opened new theories about the interaction between organisms and their environment. In this context, the work of Bruce Lipton stands out as one of the most influential yet controversial contributions to the contemporary understanding of genetic determinism. As a former professor of cellular biology, Lipton challenges the dominant dogma of molecular biology, which asserts that genetic material exclusively determines the structure and function of living beings. He proposes a model in which the cell membrane plays a key role in the interaction between the organism and its environment, suggesting that our beliefs and perceptions can directly influence biochemical processes and gene expression. This paper analyzes Lipton's theories, critically examines them, and explores their implications for the future of medicine, emphasizing the tension between mechanistic and holistic approaches to health and disease.

## REVOLUTION IN GENE UNDERSTANDING: LIPTON'S EPIGENETIC TURN

Bruce Lipton is a biologist and author known for his controversial ideas on epigenetics and consciousness. His books, such as The Biology of Belief, explore the connection between thought and biological processes. Lipton asserts that our beliefs and perceptions can influence our genes and cellular biology, an idea that diverges from traditional molecular biology. Before his career as an author, he worked as a professor of cellular biology at a medical school. His portrait is shown in the following figure..

**Figure 1.** Bruce Lipton, molecular biologist
Source: https://www.edurazvoj.com/da-li-geni-odredjuju-sudbinu-deteta-ili-je-za-to-odgovorna-okolina-epigenetika-daje-odgovor/

razumevanju genetskog determinizma. Kao bivši profesor ćelijske biologije na Medicinskom fakultetu Univerziteta Stanford i istraživač na Medicinskom fakultetu Univerziteta Wisconsin, Lipton je razvio teorije koje preispituju dominantni centralni dogmat molekularne biologije, prema kojem genetski materijal diktira strukturu i funkciju živih organizama [1].

Liptonov epigenetski preokret počinje njegovim radikalnim odstupanjem od genetskog determinizma koji je dominirao biološkim naukama od otkrića DNK. Umesto da prihvati gene kao primarne kontrolore bioloških procesa, on ističe ćelijsku membranu kao ključni interfejs između organizma i okruženja, sugerišući da signali iz spoljašnje sredine predstavljaju glavni mehanizam regulacije genetske ekspresije. U svojoj knjizi "Biologija verovanja", Lipton iznosi stav da DNK nije 'mozak' ćelije, već da ćelijska membrana reaguje na stimuluse iz okoline i prenosi signale koji uzrokuju epigenetske promene [1].

Središnji element Liptonovog epigenetskog preokreta jeste teza da naša percepcija i uverenja mogu direktno uticati na biohemijske procese u organizmu, menjajući način ekspresije naših gena. Oslanjajući se na istraživanja u psihoneuroimunologiji, Lipton tvrdi da psihološki faktori, poput stresa i emocija, mogu izazvati biološke promene kroz epigenetske mehanizme [2]. Ovaj pristup predstavlja izazov klasičnom biomedicinskom modelu, sugerišući da duh i psihološki procesi mogu modifikovati materiju na fundamentalnom nivou.

Liptonova istraživanja u oblasti matičnih ćelija dodatno potkrepljuju njegove teorije o uticaju okruženja na ćelijsko ponašanje. Kroz eksperimente je pokazao kako identične matične ćelije, izložene različitim sredinama, mogu razviti različite ćelijske tipove, uprkos identičnom genetskom materijalu [3]. Ovi nalazi naglašavaju fleksibilnost genetske ekspresije i značaj epigenetike kao mehanizma adaptacije na spoljašnje uslove.

Revolucionarnost Liptonovih ideja ogleda se u njegovom holističkom pristupu, koji povezuje različite naučne discipline. Njegovo povezivanje kvantne fizike, ćelijske biologije, psihologije i duhovnosti predstavlja pokušaj stvaranja integrisanog okvira za razumevanje života, što izaziva skepticizam u nekim naučnim krugovima [4]. Ipak, ovakva interdisciplinarnost otvara nove perspektive i postavlja pitanja koja konvencionalni pristupi mogu previđati.

Lipton takođe naglašava evolutivni značaj epigenetskih mehanizama, sugerišući da omogućavaju brže prilagođavanje promenljivim uslovima nego klasična genetska selekcija. Njegov pristup izaziva neodarvinističku sintezu koja se oslanja na slučajne mutacije i prirodnu selekciju, predlažući da organizmi poseduju sofisticirane mehanizme za aktivno prilagođavanje svom okruženju kroz epigenetske modifikacije [5].

Epigenetski preokret koji zagovara Lipton ima duboke implikacije za medicinu i terapiju. Prihvatanje ideje da naša uverenja i percepcije imaju biohemijske posledice otvara prostor za komplementarne pristupe lečenju koji uključuju psihološke i duhovne komponente [3]. Iako su njegove teorije kontroverzne, Liptonov doprinos razumevanju epigenetike ne može biti zanemaren, inspirisajući nove generacije naučnika da preispituju postojeće dogme.

Liptonov epigenetski preokret poziva nas na promenu paradigme u razumevanju života, podstičući nas da razmišljamo o sopstvenom potencijalu za samoisceljenje i odgovornosti za naše zdravlje [6]. Njegova teorija otvara nove horizonte istraživanja koja mogu voditi ka celovitijem razumevanju složenih bioloških sistema i njihove interakcije sa okruženjem.

## UM IZNAD MATERIJE: CENTRALNE POSTAVKE LIPTONOVE "BIOLOGIJE VEROVANJA"

Brus Lipton, u svojoj knjizi "Biologija verovanja" (2005) iznosi revolucionarnu tezu prema kojoj naša uverenja i percepcije direktno utiču na genetsku ekspresiju i fiziologiju ćelija. Ova perspektiva izaziva tradicionalni biomedicinski model determinizma DNK, naglašavajući da ćelijska membrana igra ključnu ulogu kao "mozak" ćelije, posredujući između spoljašnjeg okruženja i unutrašnjih biohemijskih procesa. Lipton tvrdi da signali iz okruženja, uključujući one uzrokovane našim mislima i uverenjima, mogu značajno uticati na ekspresiju gena [1].

Lipton razvija koncept da su uverenja energetski filteri koji oblikuju našu biohemijsku stvarnost. Njegova istraživanja pokazuju da stanje uma može modifikovati ćelijsko ponašanje putem složenih sistema transdukcije

Over the past decades, the understanding of genetics has undergone significant shifts, leading to a reevaluation of traditional paradigms in molecular biology. In this context, the work of Bruce Lipton represents one of the most controversial contributions to contemporary understandings of genetic determinism. As a former professor of cell biology at the Stanford University School of Medicine and a researcher at the University of Wisconsin Medical School, Lipton developed theories challenging the dominant central dogma of molecular biology, which posits that genetic material solely dictates the structure and function of living organisms [1].

Lipton's epigenetic paradigm shift begins with his radical departure from genetic determinism, which has dominated biological sciences since the discovery of DNA. Rather than accepting genes as the primary controllers of biological processes, he emphasizes the cell membrane as the key interface between the organism and its environment, suggesting that signals from the external environment are the main mechanism regulating genetic expression. In his book The Biology of Belief, Lipton argues that DNA is not the "brain" of the cell; instead, the cell membrane responds to environmental stimuli and transmits signals that induce epigenetic changes [1].

A central element of Lipton's epigenetic shift is the thesis that our perceptions and beliefs can directly influence biochemical processes in the body, altering the way our genes are expressed. Drawing on research in psychoneuroimmunology, Lipton claims that psychological factors such as stress and emotions can trigger biological changes through epigenetic mechanisms [2]. This approach challenges the classical biomedical model, suggesting that the mind and psychological processes can modify matter at a fundamental level.

Lipton's research in stem cell biology further supports his theories on environmental influence on cellular behavior. Through experiments, he demonstrated that identical stem cells, when exposed to different environments, could develop into different cell types despite having the same genetic material [3]. These findings underscore the flexibility of genetic expression and the importance of epigenetics as a mechanism for adaptation to external conditions.

The revolutionary aspect of Lipton's ideas lies in his holistic approach, linking diverse scientific disciplines. His integration of quantum physics, cell biology, psychology, and spirituality represents an attempt to create a unified framework for understanding life, which has generated skepticism in some scientific circles [4]. Nonetheless, such interdisciplinarity opens new perspectives and raises questions that conventional approaches may overlook.

Lipton also highlights the evolutionary significance of epigenetic mechanisms, suggesting that they enable faster adaptation to changing conditions than classical genetic selection. His approach proposes a neo-Darwinian synthesis that incorporates random mutations and natural selection while asserting that organisms possess sophisticated mechanisms for actively adapting to their environment through epigenetic modifications [5].

The epigenetic shift advocated by Lipton has profound implications for medicine and therapy. Accepting that beliefs and perceptions have biochemical consequences opens the door for complementary treatment approaches that integrate psychological and spiritual components [3]. Although his theories are controversial, Lipton's contribution to understanding epigenetics cannot be ignored, inspiring new generations of scientists to challenge established dogmas.

Lipton's epigenetic paradigm calls for a shift in the way we understand life, encouraging reflection on our potential for self-healing and responsibility for our health [6]. His theory opens new horizons for research that may lead to a more comprehensive understanding of complex biological systems and their interactions with the environment.

## MIND OVER MATTER: CENTRAL PREMISES OF LIPTON'S THE BIOLOGY OF BELIEF

In his book The Biology of Belief (2005), Bruce Lipton presents a revolutionary thesis asserting that our beliefs and perceptions can directly influence genetic expression and cellular physiology. This perspective challenges the traditional biomedical model of DNA determinism, emphasizing that the cell membrane functions as the "brain" of the cell, mediating between the external environment and internal biochemical processes. Lipton

signala. Na osnovu eksperimenta sa ćelijskim kulturama, Lipton sugeriše da pozitivna uverenja mogu poboljšati zdravlje, dok negativni mentalni obrasci mogu doprineti razvoju bolesti [7]. Jedna od ključnih tačaka u Liptonovoj teoriji je rekonstrukcija odnosa između svesti i biologije. On odbacuje mehanički model ljudskog tela, zamenjujući ga modelom u kojem su misli i uverenja fundamentalni faktori zdravlja. Lipton tvrdi da možemo svesno reprogramirati našu DNK promenom uverenja, uvodeći koncept "epigenetskog inženjeringa" za promenu štetnih podsvesnih uverenja, često nastalih u detinjstvu [2].

U kritici tradicionalne genetike, Lipton se oslanja na naučna otkrića iz projekta ljudskog genoma, koji je pokazao manji broj gena nego što se ranije smatralo. Ovo sugeriše da genetski materijal ne može u potpunosti objasniti kompleksnost ljudske fiziologije. Umesto toga, on naglašava ulogu epigenetskih mehanizama, koji utiču na ekspresiju gena bez promene DNK sekvence, što ukazuje na to da je okolina ključni faktor u manifestaciji genetskog potencijala [7].

Lipton povezuje individualne epigenetske procese sa širim društvenim i evolucijskim pitanjima, tvrdeći da prolazimo kroz evolutivnu prekretnicu u kojoj kolektivna svest može prevazići biološka ograničenja. U knjizi "Spontana evolucija", koju je napisao sa Stivom Baermanom, istražuju kako kolektivna uverenja oblikuju ne samo individualno zdravlje, već i evolucijski put ljudske vrste. Za Liptona, razumevanje veze između uma i biologije je ključno za poboljšanje ljudskog zdravlja i razvoj novog modela medicine koji priznaje moć uma nad materijom [2].

## POD LUPOM NAUKE: KRITIČKA ANALIZA LIPTONOVIH TVRDNJI

Naučna zajednica je zauzela složen stav prema teorijama epigenetike koje je izneo Brus Lipton. Mnogi stručnjaci priznaju određene temeljne uvide koje on nudi, ali istovremeno izražavaju ozbiljne rezerve prema njegovim daljim zaključcima. Liptonove tvrdnje o moći svesti da direktno utiče na gensku ekspresiju kroz koncept "nove biologije" značajno su izvan onoga što je trenutno dokazano u savremenim istraživanjima. Posebno su molekularni biolozi kritični prema njegovom pojednostavljenom tumačenju ćelijskih mehanizama i prenaglašavanju uloge ćelijske membrane kao "pravog ćelijskog mozga", što predstavlja značajno odstupanje od prihvaćenih modela ćelijske biologije [8].

Fundamentalni problem u Liptonovim teorijama leži u njegovom metodološkom pristupu. Dok konvencionalna nauka zahteva rigorozno testiranje hipoteza, statističku validaciju i ponovljivost rezultata, Liptonove tvrdnje često se oslanjaju na anegdotalne dokaze i selektivno tumačenje naučne literature. Kritike su posebno usmerene na njegov zaključak da misli i uverenja mogu direktno reprogramirati naše gene, što predstavlja preveliko pojednostavljenje složenih epigenetskih mehanizama dokumentovanih u naučnim istraživanjima [9].

Iako je uticaj stresa i drugih psiholoških faktora na fiziologiju nesumnjivo stvaran i dokazan kroz psihoneuroimunologiju, Lipton proširuje ove nalaze daleko izvan empirijski potvrđenog opsega. Naučna istraživanja ukazuju na to da psihološki faktori mogu uticati na biohemijske puteve koji mogu dovesti do epigenetskih promena, ali ne pružaju podršku tvrdnji da svest može direktno i voljno menjati DNK bez posrednih bioloških procesa. Ovaj raskorak između dokazanih mehanizama i Liptonovih tvrdnji predstavlja glavni razlog za skepticizam naučne zajednice [10].

Pored toga, značajan deo kritike usmeren je na Liptonovo selektivno korišćenje kvantne fizike za potporu svojih bioloških teorija. Primena kvantnih principa na makroskopske biološke sisteme predstavlja problematično pojednostavljenje koje zanemaruje razlike u razmeri i kompleksnosti između kvantnih i ćelijskih sistema. Fizičari i biolozi se uglavnom slažu da, iako kvantni efekti mogu imati ulogu u određenim biološkim procesima poput fotosinteze ili magnetorecepcije, Liptonovo proširivanje ovih fenomena na objašnjenje moći svesti preko kvantne mehanike nije potkrepljeno empirijskim dokazima [11].

Važno je napomenuti da kritički stav prema Liptonovim teorijama ne znači potpuno odbacivanje značaja epigenetike ili psiho-neuro-imunoloških veza. Naprotiv, ova polja predstavljaju uzbudljiva istraživačka područja sa rastućim brojem dokaza. Međutim, naučna zajednica insistira na preciznijem razgraničavanju između dokazanih činjenica i spekulativnih hipoteza. Trenutni naučni konsenzus priznaje složene interakcije između uma i tela, ali zadržava skepticizam prema

argues that environmental signals—including those generated by our thoughts and beliefs—can significantly impact gene expression [1].

Lipton develops the concept that beliefs act as energetic filters shaping our biochemical reality. His research suggests that the state of mind can modify cellular behavior through complex signal transduction systems. Based on experiments with cell cultures, Lipton proposes that positive beliefs can enhance health, while negative mental patterns may contribute to disease development [7]. One key aspect of Lipton's theory is the reconstruction of the relationship between consciousness and biology. He rejects the mechanistic model of the human body, replacing it with a model in which thoughts and beliefs are fundamental determinants of health. Lipton asserts that we can consciously reprogram our DNA by changing beliefs, introducing the concept of "epigenetic engineering" to modify harmful subconscious beliefs, often formed during childhood [2].

In critiquing traditional genetics, Lipton relies on findings from the Human Genome Project, which revealed a smaller number of genes than previously expected. This suggests that genetic material alone cannot fully explain the complexity of human physiology. Instead, he emphasizes the role of epigenetic mechanisms, which affect gene expression without altering the DNA sequence, highlighting the environment as a critical factor in manifesting genetic potential [7].

Lipton links individual epigenetic processes to broader social and evolutionary considerations, arguing that humanity is undergoing an evolutionary shift in which collective consciousness may overcome biological limitations. In the book Spontaneous Evolution, co-authored with Steve Bhaerman, they explore how collective beliefs shape not only individual health but also the evolutionary trajectory of the human species. For Lipton, understanding the connection between mind and biology is essential for improving human health and developing a new model of medicine that recognizes the power of the mind over matter. [2].

**UNDER THE SCIENTIFIC LENS: A CRITICAL ANALYSIS OF LIPTON'S CLAIMS**

The scientific community has taken a nuanced stance toward the epigenetic theories proposed by Bruce Lipton. While many experts acknowledge some of the foundational insights he offers, they simultaneously express serious reservations about his broader conclusions. Lipton's assertions regarding the power of consciousness to directly influence gene expression through the concept of a "new biology" significantly exceed what is currently supported by contemporary research. Molecular biologists, in particular, are critical of his simplified interpretation of cellular mechanisms and the overstated role of the cell membrane as the "true brain" of the cell, which departs markedly from accepted models of cell biology [8].

A fundamental issue with Lipton's theories lies in his methodological approach. Conventional science requires rigorous hypothesis testing, statistical validation, and reproducibility of results, whereas Lipton's claims often rely on anecdotal evidence and selective interpretation of scientific literature. Critiques are particularly directed at his conclusion that thoughts and beliefs can directly reprogram our genes, which oversimplifies the complex epigenetic mechanisms documented in empirical research [9].

Although the impact of stress and other psychological factors on physiology is real and well-established through psychoneuroimmunology, Lipton extends these findings far beyond empirically validated boundaries. Scientific studies indicate that psychological factors can influence biochemical pathways that may lead to epigenetic changes, but they do not support claims that consciousness can directly and voluntarily alter DNA without intermediary biological processes. This gap between established mechanisms and Lipton's assertions represents the primary reason for scientific skepticism [10].

Moreover, a significant portion of the criticism focuses on Lipton's selective use of quantum physics to support his biological theories. Applying quantum principles to macroscopic biological systems constitutes a problematic simplification that overlooks the scale and complexity differences between quantum and cellular systems. Physicists and biologists generally agree that while quantum effects may play a role in certain biological processes, such as photosynthesis or magnetoreception, Lipton's extension of these phenomena to explain the power of

pojednostavljenim objašnjenjima koja ne uspevaju da adekvatno obuhvate kompleksnost bioloških sistema [12]. Kritike Liptonovih teorija ukazuju na širi izazov u nauci – balansiranje između otvorenosti za nove ideje i održavanja rigoroznih standarda dokaza. Iako neki aspekti njegovih teorija mogu inspirisati nova istraživačka pitanja, naučna evaluacija zahteva da takve hipoteze budu testirane kroz sistematska istraživanja pre nego što budu široko prihvaćene. Ovaj epistemološki oprez ne predstavlja odbijanje inovativnog mišljenja, već odraz naučne metodologije koja teži ka robusnim i ponovljivim nalazima [13].

## NA GRANICI PARADIGMI: IMPLIKACIJE LIPTONOVIH TEORIJA ZA BUDUĆNOST MEDICINE

Trenutna situacija u savremenoj medicini se nalazi na raskrsnici između mehanicističkog modela i holističkih pristupa. Teorije Brusa Liptona o epigenetici zauzimaju sve značajniju, iako kontroverznu, poziciju u ovom kontekstu. Lipton tvrdi da ćelije reaguju na percepciju okruženja, a ne samo na genetsku predeterminaciju, što otvara nova razumevanja mehanizama bolesti i lečenja [1].

Centralno pitanje koje se postavlja jeste šta primarno određuje zdravlje – geni ili okolina. Dok tradicionalna genetika naglašava genetsku determinisanost, Liptonova interpretacija epigenetike fokusira se na percepciju i verovanja kao ključne faktore u biološkim procesima. Ovaj pristup može transformisati medicinsku praksu iz sistema koji se fokusira na simptome prema onome koji uzima u obzir mentalna stanja i uticaje okruženja na fiziološke procese [8].

Istraživanja u psihoneuroimunologiji i neuroendokrinologiji pružaju empirijsku podršku nekim aspektima Liptonovih teorija, posebno u vezi sa stresom i imunološkim sistemom. Hronični stres pokazuje da može uticati na ekspresiju gena putem epigenetskih modifikacija, što dodatno potvrđuje značaj psiholoških faktora u biološkom funkcionisanju [14].

Ipak, naučna zajednica ostaje oprezna prema Liptonovim širim zaključcima.
Integrativna medicina, koja kombinuje konvencionalne medicinske prakse sa komplementarnim pristupima kao što su kontrola stresa i psihološke intervencije, možda predstavlja prvi korak ka praktičnoj primeni Liptonovih principa. Ovaj pristup priznaje ulogu psiholoških faktora u fizičkom zdravlju, iako ne prihvata u potpunosti Liptonove teorije [15].

Pitanje placebo efekta dodatno ilustruje značaj Liptonovih teorija. Ovaj fenomen, koji se ranije smatrao metodološkim problemom, sve više se prepoznaje kao važan aspekt koji ukazuje na moć uverenja u modifikaciji fizioloških procesa. Liptonove teorije o percepciji mogu pomoći u razumevanju ovog fenomena, iako još uvek nedostaju definitivna objašnjenja mehanizama koji povezuju uverenja sa epigenetskim modifikacijama [16].

Bioetički izazovi su takođe važna dimenzija Liptonovih teorija. Ako prihvatimo da percepcija može uticati na zdravlje, postavlja se pitanje odgovornosti – ko je odgovoran za bolest i izlečenje? To može osnažiti pacijente, ali takođe nosi rizik od prebacivanja krivice na pojedince za stanja izvan njihove kontrole [17]. Obrazovanje zdravstvenih radnika moraće da evoluira u svetlu Liptonovih teorija. Trenutni kurikulumi fokusirani su na molekularne aspekte, dok bi integracija epigenetskih principa mogla obogatiti buduće lekare razumevanjem interakcije između uma, tela i okruženja [18].

Osporavanje Liptonovih teorija ne znači potpuno odbacivanje veze između uma i tela, već poziv na preciznija istraživanja. Ideja da psihološki faktori utiču na fiziologiju kroz epigenetske mehanizme predstavlja legitimno istraživačko polje [19]. Liptonov doprinos možda nije u konkretnim mehanizmima, već u izazivanju postojećih paradigmi i podsticanju istraživanja koje prevazilazi trenutne granice. Bez obzira na to da li će njegove teorije izdržati test vremena, njegova sposobnost da pokrene dijalog između različitih pristupa zdravlju predstavlja značajan doprinos evoluciji [20].

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consciousness via quantum mechanics is not empirically substantiated [11].

It is important to note that critical perspectives on Lipton's theories do not imply a wholesale rejection of epigenetics or psychoneuroimmunological connections. On the contrary, these fields represent exciting areas of research with a growing body of evidence. However, the scientific community insists on a precise distinction between established facts and speculative hypotheses. The current scientific consensus acknowledges the complex interactions between mind and body but remains skeptical of simplified explanations that fail to adequately account for the intricacy of biological systems [12]. Critiques of Lipton's theories highlight a broader challenge in science—balancing openness to novel ideas with the maintenance of rigorous standards of evidence. While some aspects of his theories may inspire new research questions, scientific evaluation requires that such hypotheses undergo systematic investigation before they are widely accepted. This epistemological caution does not represent a rejection of innovative thinking but rather reflects a scientific methodology committed to robust and reproducible findings. [13].

**AT THE EDGE OF PARADIGMS: IMPLICATIONS OF LIPTON'S THEORIES FOR THE FUTURE OF MEDICINE**

Contemporary medicine stands at a crossroads between the mechanistic model and holistic approaches. Bruce Lipton's epigenetic theories occupy an increasingly prominent, albeit controversial, position within this context. Lipton asserts that cells respond to environmental perception rather than solely to genetic predetermination, opening new understandings of disease mechanisms and treatment strategies [1].

The central question raised is what primarily determines health—genes or environment. While traditional genetics emphasizes genetic determinism, Lipton's interpretation of epigenetics focuses on perception and beliefs as key modulators of biological processes. This approach has the potential to transform medical practice from a system centered on symptoms to one that considers mental states and environmental influences on physiological processes [8].

Research in psychoneuroimmunology and neuroendocrinology provides empirical support for some aspects of Lipton's theories, particularly regarding stress and the immune system. Chronic stress has been shown to influence gene expression through epigenetic modifications, further highlighting the importance of psychological factors in biological functioning [14].

However, the scientific community remains cautious about Lipton's broader conclusions.

Integrative medicine, which combines conventional medical practices with complementary approaches such as stress management and psychological interventions, may represent the first practical application of Lipton's principles. This approach acknowledges the role of psychological factors in physical health, although it does not fully endorse Lipton's theories [15].

The placebo effect further illustrates the relevance of Lipton's ideas. Once considered merely a methodological confound, it is increasingly recognized as a phenomenon demonstrating the power of belief to modify physiological processes. Lipton's theories on perception may help explain this effect, although definitive mechanisms linking beliefs to epigenetic modifications remain unestablished [16].

Bioethical challenges also arise from Lipton's perspective. Accepting that perception can influence health raises questions of responsibility—who is accountable for illness and recovery? While this may empower patients, it also carries the risk of attributing blame to individuals for conditions beyond their control [17]. Medical education will need to evolve in light of Lipton's theories. Current curricula emphasize molecular aspects, whereas integrating epigenetic principles could enrich future physicians' understanding of the mind-body-environment interplay [18].

Critiquing Lipton's theories does not imply rejecting the mind-body connection; rather, it calls for more precise research. The concept that psychological factors influence physiology through epigenetic mechanisms represents a legitimate field of investigation [19]. Lipton's contribution may lie less in providing concrete mechanisms and more in challenging existing paradigms and stimulating research that transcends current boundaries.

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Regardless of whether his theories withstand the test of time, his ability to provoke dialogue between different approaches to health represents a meaningful contribution to the evolution of medicine. [20].

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# DOKTOR ĐORĐE JOANOVIĆ, PRVI SRPSKI ONKOLOG

*Dijana Piljić*

DOM ZDRAVLJA NOVI BEČEJ, NOVI BEČEJ

**Sažetak**: Đorđe Joanović rođen je 16. juna 1871. godine u Beču, od oca Haritona i majke Marije. Poreklo porodice Joanović vodi iz sela Beodre. Svoj naučni rad i karijeru na Univerzitetu u Beču je prekinuo i po završetku Prvog svetskog rata došao u Beograd u patriotskoj želji da pomogne ratom razorenoj Srbiji. Doktor Đorđe Joanović bio je naučnik svetskog glasa i jedan od pionira u oblasti laboratorijskog izučavanja onkoloških oboljenja i epidemiologije karcinogeneze. Bio je osnivač Medicinskog fakulteta u Beogradu, inicijator osnivanja Instituta za patologiju u Beogradu, osnivač i predsednik Jugoslovenskog društva za izučavanje i suzbijanje raka i dekan Medicinskog fakulteta u Beogradu. Profesor doktor Đorđe Joanović je bio dopisni član Kraljavske srpske akademije nauka, počasni član Matice srpske u Novom Sadu, stalni delegat Kraljevine Jugoslavije pri Međunarodnom ofisu za javnu higijenu u Parizu, član nemačkog i češkog onkološkog Komiteta za suzbijanje raka, član redakcije brojnih medicinskih časopisa, predsednik Srpskog lekarskog društva, predsednik Jugoslovenskog lekarskog društva, predavač za vojni sanitet i član Sanitetskog saveta Vojske Kraljevine Jugoslavije, predsednik fonda za pomoć siromašnim studentima, član Komiteta međinarodnog instituta za geografsku patologiju, urednik Srpskog arhiva za celokupnu medicinu, predstavnik Kraljevine Jugoslavije u Sveslovenskom lekarskom savezu. Institut za patologiju u Beogradu, Osnovna škola u Novom Miloševu i Opšta bolnica u Zrenjaninu nose ime "Doktor Đorđe Joanović".
**Ključne reči:** doktor Đorđe Joanović, Institut za patologiju Beograd, onkologija, epidemiologija kancerogeneze

## UVOD

Profesor doktor Đorđe Joanović je utemeljivač onkologije i eksperimentalne patologije u Srbiji. On je prvi srpski onkolog. Doktor Đorđe Joanović imao je najviše univerzitetsko zvanje i poziciju od svih Srba u svetu tog vremena, posebno zainteresovan za eksperimentalnu onkologiju i patologiju, kao i onkološku patologiju i patološku morfologiju. Doprinos profesora doktora Đorđa Joanovića razvoju medicine, a pogotovo onkologije u Srbiji je od nemerljivog značaja. Naučni rad profesora doktora Đorđa Joanovića u domenu eksperimentalne patologije i imunopatologije bio je pionirski i u svetskim razmerama, tako da je imao impresivnu svetsku reputaciju. Posvetio se eksperimentima kod onkoloških oboljevanja i izučavao epidemiologiju karcinogeneze. Sa naročitim se zanimanjem profesor Đorđe Joanović bavio studijama o patološkim promenama tkiva kod različitih oboljenja, uvek pri tome poklanjajući veliku i osobitu pažnju patološkoj anatomiji i histologiji. Profesor stekao reputaciju jednog od najznačajnijih naučnika u svetskim razmerama, svojim postupcima i delima nam je pokazao šta znači patriotizam i rodoljublje.

## PORODICA JOANOVIĆ

Doktor Đorđe Joanović rođen je u Beču od majke Marije i oca Harintona. Majka Marija rođena je Vlahović, poreklom iz Velikog Bečkereka. Otac Harinton rođen je u Beodri. Danas je Beodra naselje u okviru sela Novo Miloševo. Preci porodice Joanović vode poreklo iz južne srpske pokrajne, Kosova i Metohije. Deda Đorđa Joanovića je Aksentije Joanović koji je bio pravoslavni sveštenik i paroh pravoslavne crkvene opštine u Beodri. Aksentije je bio dobar prijatelj sa pravoslavnim sveštenikom Dionisijem Jakšićem, koji je bio rodom iz susednog sela Karlova. Dionisije Jakšić je bio otac našeg pesnika i slikara Đure Jakšića. Sinovi Aksentija i Dionisija, Harinton Joanović i Đura Jakšić, družili su se u detinjstvu i postali dobri drugovi.


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# DR. ĐORĐE JOANOVIĆ, THE FIRST SERBIAN ONCOLOGIST

*Dijana Piljić*

PRIMARY HEALTH CARE CENTER "NOVI BEČEJ", NOVI BEČEJ

**Summary:** Đorđe Joanović was born on June 16, 1871, in Vienna, to father Hariton and mother Marija. The Joanović family originates from the village of Beodra. He interrupted his scientific work and career at the University of Vienna and, after the end of World War I, moved to Belgrade out of a patriotic desire to help war-torn Serbia. Dr. Đorđe Joanović was a world-renowned scientist and one of the pioneers in laboratory research on oncological diseases and the epidemiology of carcinogenesis. He was the founder of the University of Belgrade Faculty of Medicine, the initiator of the establishment of the Institute of Pathology in Belgrade, founder and president of the Yugoslav Society for the Study and Suppression of Cancer, and dean of the Faculty of Medicine in Belgrade. Professor Dr. Đorđe Joanović was a corresponding member of the Royal Serbian Academy of Sciences, an honorary member of Matica Srpska in Novi Sad, permanent delegate of the Kingdom of Yugoslavia to the International Office of Public Hygiene in Paris, member of the German and Czech Oncology Committees for Cancer Control, member of the editorial boards of numerous medical journals, president of the Serbian Medical Society, president of the Yugoslav Medical Society, lecturer for the military medical service, and member of the Sanitary Council of the Army of the Kingdom of Yugoslavia. He was also president of the fund for assisting poor students, member of the Committee of the International Institute for Geographical Pathology, editor of the Serbian Archive of General Medicine, and representative of the Kingdom of Yugoslavia in the All-Slavic Medical Union. The Institute of Pathology in Belgrade, the elementary school in Novi Miloševo, and the General Hospital in Zrenjanin bear the name "Dr. Đorđe Joanović."

**Keywords:** Dr. Đorđe Joanović, Institute of Pathology, Belgrade – Oncology, Epidemiology of Carcinogenesis

## INTRODUCTION

Professor Dr. Đorđe Joanović is recognized as the founder of oncology and experimental pathology in Serbia. He holds the distinction of being the first Serbian oncologist. At his time, Dr. Joanović attained the highest academic rank and position among Serbs worldwide, with a particular focus on experimental oncology, pathology, oncological pathology, and pathological morphology. His contributions to the development of medicine, especially oncology in Serbia, are of immeasurable significance.

Professor Dr. Joanović's scientific work in experimental pathology and immunopathology was pioneering even on a global scale, earning him an impressive international reputation. He dedicated himself to experiments on oncological diseases and studied the epidemiology of carcinogenesis. With special interest, he conducted studies on pathological changes in tissues across various diseases, always giving careful and meticulous attention to pathological anatomy and histology.

Professor Joanović earned a reputation as one of the most important scientists globally, demonstrating through his work and actions the true meaning of patriotism and devotion to one's country.

## THE JOANOVIĆ FAMILY

Dr. Đorđe Joanović was born in Vienna to his mother Marija and father Harinton. His mother, Marija, née Vlahović, was originally from Veliki Bečkerek. His father, Harinton, was born in Beodra, which today is a settlement within the village of Novo Miloševo.

The Joanović family traces its ancestry to the southern Serbian province of Kosovo and Metohija. Đorđe Joanović's grandfather, Aksentije Joanović, was an Orthodox priest and parish priest of the Orthodox church community in Beodra. Aksentije was a close friend of Dionisije Jakšić, an Orthodox priest from the neighboring village of Karlova. Dionisije Jakšić

**Slika 1.** Pravoslavni sveštenik Aksentije Joanović i pravoslavni sveštenik Dionisije Jakšić

Aksentije je svog sina Harintona poslao na školovanje u Beč, gde je Harinton diplomirao advokaturu i tamo ostao da živi i radi. Cela porodica Joanović je bar jednom godišnje posećivala rodno mesto Beodru. Harinton Joanović (1824.-1884.) advokat i senator, bio je upravnik "Austrijskog železničkog magnata" bečkog barona Sine u Beču. Harinton se u Beču oženio i sa svojom suprugom Marijom 1868. godine i dobio dva sina: Đorđa i Simeona Joanovića. U domu Joanovića negovala se tradicija, te su Đorđe i Simeon odgajani u patrijahalnom duhu stare srpske tradicije. Za kuma na krštenju svojih sinova Harinton bira bečkog barona Sina. Otac Đorđa Joanovića, Harinton i majka Marija, ostali su zapamćeni kao veliki dobrotvori. Đura Jakšić je došao u Beč 1852. godine da nastavi svoje studije slikarstva, tako da se njihovo drugarstvo iz detinjstva u Beodri nastavilo i u Beču. Đura Jakšić je čitavu godinu u kući Haritona i Marije Joanović imao stan i hranu. Oba Harintonova, sina Đorđe i Simeon su završila visoke škole u Beču. Đorđe Joanović je postao profesor na Medicinskom fakultetu u Beču, a Simeon Joanović konzul Kraljevine Srbije u Beču. Brat Simeon Joanović (1868.-1934.) je bio austrijski vicekonzul u Beogradu (1885.-1897.), pa od 1901. godine civilni komesar Austrougarske u Pljevljima, gde je Đorđe Jonović kao Austrougarski podanik 1897. godine imenovan za načelnika novoizgrađene vojne bolnice na Stažici u Pljevljima. Simeon Joanović austrougarski, dvadest dve godine civilni komesar za Srez Pljevlja po odlasku u penziju je autor višedelne knjige "Novopazarski sandžak 1878.-1900.".

Simeon Joanović je duže vreme živeo u Beogradu i Cirihu. Nakon života u ovim gradovima vratio se sa suprugom Anom na porodično imanje u Beodri. Tamo ga je često posećivao doktor Đorđe Joanović. Porodica Joanović bila je poštovana i cenjena u svom rodnom selu. Profesora doktora Đorđa Joanovića meštani su zvali doktor Đoka.

**Slika 2.** Profesor doktor Đorđe Joanović

## BIOGRAFIJA DOKTORA ĐORĐA JOANOVIĆA

### *Školovanje doktora Đorđa Joanovića*

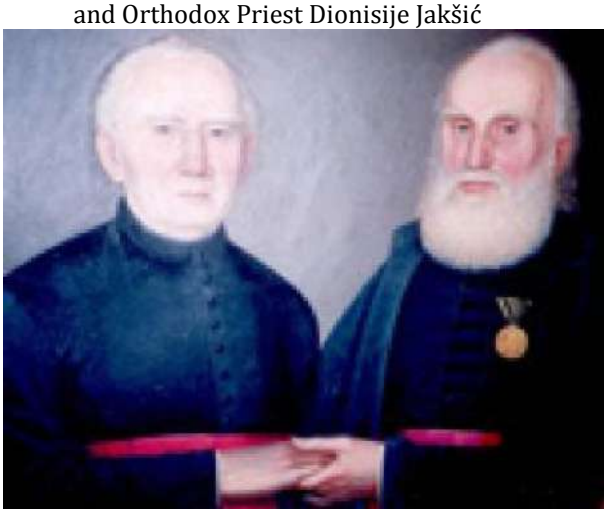
Osnovnu školu je Đorđe Joanović završio u Beču, a zatim se upisao u veoma cenjenu Bečku gimnaziju "Kaizer und Konig" gde je maturirao 1889. godine. Upisao je Medicinski fakultet u Beču i diplomirao 1895. godine. Odmah po završetku studija zapošljava se na istom fakultetu kao asistent od 1895. do 1899. godine u Institutu za patološku histologiju i bakteriologiju. Zatim se opet kao asistent prebacio na Institut za opštu i eksperimentalnu patologiju i tu radio od 1899.-1904. godine. Radio je uz čuvenog patologa, profesora Paltaufa (1858.-1924.) koji je bio Pasterov i Kohov učenik. Za docenta je proglašen 1904. godine. Vanredni profesor opšte i eksperimentalne patologije na Bečkom Medicinskom fakultetu postaje 1910. godine, a radovni profesor 1919. godine. Rektor Univerziteta u Beču u to vreme bio je čuveni patolog, akademik i predsednik Akademije Karl fon Rokitanski (1804-1878.). Rivali Bečke medicinske škole u svetu bi mogli biti samo Berlin, Pariz, London, a donekle i Sankt Peterburg.

Doktor Đorđe Joanović za to vreme bio je šef Odeljenja za patologiju Opšte medicine u

was the father of the renowned Serbian poet and painter Đura Jakšić.

The sons of Aksentije and Dionisije, Harinton Joanović and Đura Jakšić, grew up together and became close childhood friends.

**Figure 1.** Orthodox Priest Aksentije Joanović and Orthodox Priest Dionisije Jakšić



Aksentije sent his son Harinton to study in Vienna, where Harinton graduated in law and remained to live and work. The entire Joanović family visited their ancestral village of Beodra at least once a year. Harinton Joanović (1824–1884), a lawyer and senator, served as manager for the "Austrian Railway Magnate" Baron Sine in Vienna. In Vienna, Harinton married his wife Marija in 1868, and they had two sons: Đorđe and Simeon Joanović.

The Joanović household upheld family traditions, and both Đorđe and Simeon were raised in the patriarchal spirit of old Serbian customs. For the godfather of his sons' baptisms, Harinton chose Baron Sine of Vienna. Đorđe's father, Harinton, and mother, Marija, were remembered as generous benefactors. In 1852, the Serbian painter and poet Đura Jakšić came to Vienna to continue his art studies, and his childhood friendship with Harinton's family from Beodra continued in Vienna. Đura Jakšić was provided with accommodation and meals in the Joanović household for an entire year.

Both of Harinton's sons, Đorđe and Simeon, completed higher education in Vienna. Đorđe Joanović became a professor at the Medical Faculty in Vienna, while Simeon Joanović served as a consul of the Kingdom of Serbia in Vienna. Simeon Joanović (1868–1934) was the Austrian vice-consul in Belgrade (1885–1897), and from 1901, the civil commissioner of Austria-Hungary in Pljevlja, where Đorđe Joanović, as an Austro-Hungarian subject, was appointed in 1897 as the head of the newly built military hospital at Stažica in Pljevlja. After retiring, Simeon Joanović authored the multi-volume book "Novopazarski Sandžak 1878–1900."

Simeon Joanović lived for extended periods in Belgrade and Zurich. Afterward, he returned with his wife Ana to the family estate in Beodra, where he was often visited by Dr. Đorđe Joanović. The Joanović family was respected and esteemed in their native village. Locals affectionately called Professor Dr. Đorđe Joanović "Doctor Đoka".

**Figure 2.** Professor Dr. Đorđe Joanović

**BIOGRAPHY OF DOCTOR ĐORĐE JOANOVIĆ**

***Education of Dr. Đorđe Joanović***

Đorđe Joanović completed his primary education in Vienna and subsequently enrolled in the highly esteemed Vienna Gymnasium "Kaiser und König," where he graduated in 1889. He then entered the Medical Faculty in Vienna, graduating in 1895. Immediately after completing his studies, he was employed at the same faculty as an assistant from 1895 to 1899 in the Institute of Pathological Histology and Bacteriology. He later moved as an assistant to the Institute of General and Experimental Pathology, where he worked from 1899 to 1904.

During this period, he worked under the renowned pathologist Professor Paltauf (1858–1924), a student of Pasteur and Koch. Joanović was appointed as a docent in 1904. He became an associate professor of general and

Beču radio napredne eksperimente iz patologije u prestižnim laboratorijama Instituta za patologiju u Beču. Narednih dvadeset pet godine bio je njihov stalni,odani i dostojni saradnik.

U to vreme je dr Đorđe Joanović imao je najviše univerzitetsko zvanje i poziciju od svih Srba u svetu, posebno zainteresovan za eksperimentalnu onkologiju i patologiju, kao i onkološku patologiju i patološku morfologiju.

***Dolazak doktora Joanovića u Srbiju***

Po završetku Prvog svetskog rata dr Milan Jovanović-Batut i dr Vojislav Subotić pozivaju doktora Đorđa Joanovića da dođe iz Beča u Srbiju i svojim stručnim znanjem i organizacionim sposobnostima pomogne osnivanju Medicinskog fakulteta u Beogradu. Doktor Đorđe Joanović se ovom pozivu odmah odaziva. Na prvoj sednici održanoj 20. 02. 1920. godine, sastao se prvi kolegijum profesora Medicinskog fakulteta u Beogradu. Za dekana je izabran doktor Milan Jovanović- Batut, a za redovnog profesora opšte patologije doktor Đorđe Joanović. Tada je doktor Joanović doneo odluku da napusti svoj naučni rad u prestižnim bečkim laboratorijama i karijeru univerzitetskog profesora u Beču. Preselio se u Beograd 06. maja 1920. godine, sa velikom željom da pomogne razvoju medicine u ratom opustošenoj Srbiji. Morao je da se nosi sa ogromnim organizacionim i drugim poteškoćama, naišao je i na neopravdane prepreke nekih ljudi.

**Slika 3.** Prvih osam profesora Medicinskog fakulteta u Beogradu; sa leva na desno: doktor Miloš Bogdanović, doktor Rihard Burijan, doktor Vladan Đorđević, doktor Pavle Popović, doktor Đorđe Joanović, doktor Milan Jovanović- Batut, doktor Milivoje Kostić i doktor Slobodan Kostić

Godine 1924. u Beču je umro profesor Rihard Paltauf. Na mesto njegove upražnjenje Univerzitetske katedre konkurisalo je dvadesetak uvaženih nemačkih patologa, ali je Fakultetski savet Medicinskog fakulteta u Beču odlučio da pozove doktora Đorđa Joanovića da se vrati u Beč i zauzme mesto profesora Paltaufa. Bilo je to veliko priznanje za stručnost i znanje koje je imao profesor doktor Đorđe Joanović. I pored loših uslova za rad koje je u to vreme imao u Beogradu, doktor Đorđe Joanović je odbio ponudu iz Beča, želeći da završi svoje projekte koje je započeo u Srbiji. Po osnivanju Medicinskog fakulteta, doktor Đorđe Joanović je radio na osnivanju Onkološke službe Kraljevine Srba Hrvata i Slovenaca i dao inicijativu i detaljnije idejne projekte za osnivanje Instituta za patologiju u Beogradu. Tri godine je trajala izgradnja u kojoj je doktor Đorđe Joanović aktivno učestvovao dajući konkretne savete. Prema nacrtima i idejama podignuta je zgrada novog Instituta za patologiju koja je bila svečano otvorena 22. aprila 1926. godine. Bila je to najsavremenija ustanova te namene u tadašnjoj Evropi. Na otvaranju ovog Instituta svečani govor održao je doktor Đorđe Joanović. Institut za patologiju u Beogradu je uskoro postao regionalni centar za eksperimentalnu patologiju. Njegovi saradnici bili su: Ksenofon Šahović (1898-1956.), Dimitrije Tihomirov, Marija Višnjić, Živojin Ignjačev i drugi. U laboratorijama Instituta je profesor doktor Đorđe Joanović radio po čitav dan. Kabinet je pretvorio u svoj stan u kojem je i živeo.

Skoro uvek u 8 sati ujutro profesor bi dolazio na obdukcije, u podne držao predavanje, a u ostalo slobodno vreme, najčešće posle podne, bavio se u zajednici sa svojim saradnicima dijagnostikovanjem histoloških preparata, za odgovor i od obdukcija. Dva puta nedeljno na kraju praktičnih histoloških vežbi profesor Đorđe Joanović skoro uvek bi lično uz projekciju objašnjavao đacima podatke za vežbe s histološkim preparatima. Bolesnici sa neoplazmama su tražili da ih pregleda doktor Joanović i tu njihovu želju uvek je zadovoljavao, dajući im iscrpni savet za lečenje a često i pismenu preporuku.

Godine 1926. postaje dopisni član Srpske kraljevske akademije nauka. Profesor doktor Đorđe Joanović je svoj život u potpunosti posvetio medicinskoj nauci i borbi protiv bolesti raka.

experimental pathology at the Vienna Medical Faculty in 1910 and a full professor in 1919. At that time, the rector of the University of Vienna was the famous pathologist and academician Carl von Rokitansky (1804–1878). The main rivals of the Vienna Medical School worldwide were Berlin, Paris, London, and to some extent St. Petersburg.

Dr. Joanović led the Department of General Medical Pathology in Vienna, conducting advanced experiments in prestigious laboratories of the Institute of Pathology. For the next twenty-five years, he remained a dedicated and respected collaborator. During this time, he held the highest academic rank and position among Serbs globally, with a particular focus on experimental oncology, pathology, oncological pathology, and pathological morphology.

***Arrival of Dr. Joanović in Serbia***

After the end of World War I, Dr. Milan Jovanović-Batut and Dr. Vojislav Subotić invited Dr. Đorđe Joanović to come from Vienna to Serbia and contribute his expertise and organizational skills to the establishment of the Medical Faculty in Belgrade. Dr. Joanović accepted the invitation without hesitation. At the first session held on February 20, 1920, the inaugural assembly of professors of the Medical Faculty in Belgrade took place. Dr. Milan Jovanović-Batut was elected dean, and Dr. Đorđe Joanović was appointed full professor of general pathology.

At that time, Dr. Joanović made the decision to leave his scientific work in prestigious Viennese laboratories and his university career in Vienna. He moved to Belgrade on May 6, 1920, with a strong desire to contribute to the development of medicine in war-torn Serbia. He faced significant organizational challenges and obstacles, including some unjust opposition from certain individuals.

**Figure 3.** The first eight professors of the Medical Faculty in Belgrade; from left to right: Dr. Miloš Bogdanović, Dr. Richard Burian, Dr. Vladan Đorđević, Dr. Pavle Popović, Dr. Đorđe Joanović, Dr. Milan Jovanović-Batut, Dr. Milivoje Kostić, and Dr. Slobodan Kostić.

In 1924, Professor Richard Paltauf passed away in Vienna. About twenty esteemed German pathologists applied to fill his university chair, but the Faculty Council of the Medical Faculty in Vienna chose to invite Dr. Đorđe Joanović to return and occupy Paltauf's position. This was a significant recognition of Dr. Joanović's expertise and knowledge. Despite difficult working conditions in Belgrade, he declined the offer, wishing to complete the projects he had begun in Serbia.

After the founding of the Medical Faculty in Belgrade, Dr. Joanović worked on establishing the Oncology Service of the Kingdom of Serbs, Croats, and Slovenes and provided the initiative and detailed conceptual plans for the Institute of Pathology in Belgrade. The construction took three years, during which he actively participated, giving concrete advice. Based on his designs and ideas, the new Institute of Pathology building was completed and officially opened on April 22, 1926. At the opening, Dr. Joanović delivered the inaugural speech. The Institute quickly became a regional center for experimental pathology. His collaborators included Ksenofon Šahović (1898–1956), Dimitrije Tihomirov, Marija Višnjić, Živojin Ignjačev, and others. Dr. Joanović spent entire days in the laboratories, even converting his office into his living quarters.

Almost every day at 8 a.m., he attended autopsies; at noon, he delivered lectures, and in his free time—usually in the afternoons—he worked with colleagues on diagnosing

U tom cilju je 27. septembra 1927. godine osnovao Jugoslovensko društvo za izučavanje i suzbijanje raka. Generalni sekretar bio je K. Šahović, tadašnji srpski akademik. U to vreme Jugoslovensko društvo za izučavanje i lečenje raka bilo je četvrto u svetu, odnosno posle Beča 1910. godine, Vašingtona 1917. godine i Pariza 1920. godine. Predstavljao je Srbiju i Jugoslaviju na brojnim medicinskim kongresima u Evropi i Sjedinjenim Američkim Državama.

Profesor doktor Đorđe Joanović bio je jedini dekan Medicinskog Fakulteta koji je na to mesto biran četiri puta (1923./1924. godine, 1925./1926. godine, 1927./1928. godine,1928./1929. godine). Doktor Đorđe Joanović je bio osnivač Udruženja jugoslovenskih medicinara čiji je bio počasni i doživotni predsednik.

Profesor Đorđe Joanović je bio predsednik Srpskog lekarskog društva i veliki prijatelj studenata medicine te je izabran i za doživotnog počasnog predsednika Saveza studenata medicine Jugoslavije. On je 1928. godine odlikovan Ordenom Svetog Save II reda. Bio je začetnik ideja da se u Beogradu osnuje Institut za onkologiju i radiologiju. Ovaj Institut je završen u jesen 1939. godine pod potkroviteljstvom Njenog Veličanstva kraljice Marije, a glavni donator je bio knez Pavle Karađorđević.

Doktor Đorđe Joanović je iz Beča poneo svoje veliko medicinsko znanje i ugled univerzitetskog profesora. Bio je poznat po svojoj stručnosti, konstruktivnosti, tačnosti i pedantnosti. Privatno je profesor doktor Đorđe Joanović voleo muziku i umetnost. Veoma često je odlazio na koncerte klasične muzike. On je i sam odlično svirao violinu. Kažu da je imao tihu i skromnu narav koja je prijala, ali i osvajala sagovornike. Njegovi student i saradnici su ga visoko poštovali, cenili i voleli. Davao je podršku studentima i bio je na njihovoj strani kada su oni protestovali i borili se za autonomiju Univerziteta.

Bio je omiljen kao profesor koji u svakoj prilici želi da razume probleme studenata, ali i da im pomogne. Međutim, njegova solidarnost sa studentima koji traže autonomiju Univerziteta ondašnjim gradskim vlastima se iz političkih razloga nije dopala. Zbog toga je ovaj stari profesor doktor Đorđe Joanović kod vlasti zapao u velike probleme. Kad je 1929. godine proglašena Obznana, situacija se na Beogradskom Univerzitetu kao i u čitavoj državi još vise zaoštrila. Nakon uvođenja "Šetojanuarske dikatature" 1929. godine režim se surovo obračunavao sa svim političkim oponentama, pa i sa onim iz redova studenata.

Profesor doktor Đorđe Joanović nije bio politički aktivan, ali je bio na strani studenata i radnika. Zbog toga je prema pojedinim svedočenjima imao 27. januara 1932. godine žučnu raspravu sa predsednikom Ministarskog saveta generalom Petrom Živkovićem, koja se završila tako što je profesora Joanovića general Živković ošamario.

Doktor Đorđe Joanović se nikada nije ženio. Na pitanje zašto se nije oženio, odgovorio je slično kao Tesla: "Kada sam započeo sa eksperimentima u patologiji, uvideo sam da nauka zahteva celog čoveka." Njegov rođeni brat, Simeon Joanović, bio je oženjen sa suprugom Anom, ali nije imao dece. Nažalost, time se loza familije Joanović ugasila.

**TRAGIČAN KRAJ**

Epilog priče o Joanoviću bio je tragičan. 1932. godine, organizujući godišnji Svetosavski studentski bal, studenti medicine javili su da je srpski kralj Aleksandar Prvi dobrodošao da dođe na bal, ali ne i njegov premijer general Petar Živković. General Petar Živković je pozvao doktora Joanovića u svoju kancelariju gde su imali žučnu raspravu. Ponižen doktor Joanović je izjurio iz kabineta Petra Živkovića i otišao u njegov Institut za patologiju, u njegovu sobu. Ujutru 28. januara 1932. godine pronađen je obešen o kvaku na prozoru i kako leži u svojoj fotelji. Poslužiteljka je zatekla beživotno telo doktora Đorđa Joanovića i odmah je pozvala svoga supruga koji je radio kao domar u zgradi Instituta. On je skinuo telo profesora sa kanapa o koji je bio obešen. Profesorka patologije, doktorka Marija Višnjić-Frajnd, izjavila je da je u ognjištu ujutru pronađeno mnogo pepela, što je značilo da je spaljivao svoje dosijee. Neočekivana smrt profesora doktora Đorđa Joanovića je sve ražalostila, ali i začudila. Okolnosti pod kojima je nastupila smrt doktora Đorđa Joanovića do danas nisu sasvim razjašnjene i kod mnogih postoji sumnja da je doktor Đorđe Joanović bio ubijen.

Smrt doktora Đorđa Joanovića izazvala je gnev među beogradskim intelektualcima jer su mnogi odmah posumnjali da je profesor zaista sam sebi oduzeo život.

histological samples. Twice a week, at the end of practical histology exercises, he personally explained the data for students using projections of histological specimens. Patients with neoplasms often requested consultations with him, which he always granted, providing comprehensive advice and frequently written recommendations.

In 1926, he became a corresponding member of the Serbian Royal Academy of Sciences. Dr. Joanović dedicated his life entirely to medical science and the fight against cancer. On September 27, 1927, he founded the Yugoslav Society for the Study and Suppression of Cancer, with K. Šahović as general secretary. At that time, this society was the fourth of its kind in the world, after Vienna (1910), Washington (1917), and Paris (1920). He represented Serbia and Yugoslavia at numerous medical congresses in Europe and the United States.

Professor Dr. Đorđe Joanović was the only dean of the Medical Faculty to be elected four times (1923/24, 1925/26, 1927/28, 1928/29). He also founded the Association of Yugoslav Physicians, serving as its honorary and lifelong president. He was president of the Serbian Medical Society and a close friend of medical students, elected as lifelong honorary president of the Yugoslav Medical Students' Union. In 1928, he was awarded the Order of Saint Sava, Second Class. He was the initiator of the idea to establish the Institute for Oncology and Radiology in Belgrade, which was completed in the autumn of 1939 under the patronage of Her Majesty Queen Maria, with Prince Pavle Karađorđević as the main donor.

Dr. Joanović brought his vast medical knowledge and university reputation from Vienna. He was known for his expertise, precision, and meticulousness. Privately, he loved music and art and was an accomplished violinist. He had a quiet and modest nature that charmed and won over his interlocutors. Students and colleagues deeply respected, valued, and loved him, appreciating his support and advocacy for student autonomy at the university.

He was especially beloved as a professor who sought to understand and help students with their problems. However, his solidarity with students seeking university autonomy displeased city authorities, leading to significant difficulties. In 1929, during the proclamation of the Obznana and the introduction of the January dictatorship, the regime harshly targeted political opponents, including students. Although not politically active, he supported students and workers. According to some reports, on January 27, 1932, he had a heated dispute with Prime Minister General Petar Živković, which ended with the general slapping him.

Dr. Đorđe Joanović never married. When asked why, he answered similarly to Nikola Tesla: "When I began experiments in pathology, I realized that science requires a whole person." His brother Simeon Joanović was married to Ana but had no children, so the Joanović family line unfortunately ended..

## TRAGIC END OF PROFESSOR DR. ĐORĐE JOANOVIĆ

The epilogue of Dr. Joanović's life was tragic. In 1932, while organizing the annual St. Sava Students' Ball, medical students informed him that King Alexander I of Serbia was welcome to attend, but not his Prime Minister, General Petar Živković. General Živković summoned Dr. Joanović to his office, where they engaged in a bitter argument. Humiliated, Dr. Joanović stormed out and returned to his Institute of Pathology, to his room. On the morning of January 28, 1932, he was found hanged from a window latch, with his body lying in his armchair. A maid discovered the lifeless body and immediately called her husband, who worked as a janitor in the Institute building. He removed Dr. Joanović's body from the rope. Professor of Pathology Dr. Marija Višnjić-Frajnd reported that a large amount of ashes was found in the fireplace that morning, indicating that he had burned his personal files. The unexpected death of Professor Dr. Đorđe Joanović caused sorrow and surprise. The circumstances of his death remain unclear, and many suspect that he may have been murdered. His death provoked outrage among Belgrade intellectuals, as many immediately doubted that the professor had taken his own life.

The Medical Faculty Council decided to hold a brief memorial service in the amphitheater of the Institute of Pathology in Belgrade, while a religious ceremony would be conducted in his native village of Beodra. His remains were transported by train, accompanied by a large number of students, friends, and colleagues. Belgrade had never before witnessed

Savet Medicinskog fakulteta doneo je odluku da se u Beogradu održi kratko opelo u amfiteatru Instituta za patologiju a da se verski obred ubavi u njegovom selu, u Beodri. Posmrtni ostaci profesora doktora Đorđa Joanovića preneti su vozom uz pratnju velikog broja njegovih studenata, prijatelja i kolega. Beograd nikada ranije nije bio svedok ovako masovne i tužne pratnje kovčega do beogradske železničke stanice na sahranu u Beodri. Na sahranu poštovanog profesora Joanovića došlo je nekoliko stotina studenata Univerziteta u Beogradu, najviše sa Medicinskog fakulteta, a vence su poslale mnoge ugledne ličnosti iz javnog života Kraljevine Jugoslavije toga doba. Doktor Đorđe Joanović sahranjen je na beodranskom groblju 29. januara 1932. Iako se sumnjalo na samoubistvo, Patrijarh srpski Varnava odobrio je da se održi opelo nad zaslužnim pokojnikom. 28. februra 1932. godine nepravedno je objavljen članak "Slučaj profesora Joanovića" čiji su autori politički protivnici doktora Đorđa Joanovića, dr Svetozar Moačanin i doktor Dušan Petrović, koji su napisali sledeće: "On je došao u Srbiju da stvara i samim tim njegova načelna gledišta na fakultet u moralnom i naučnom pogledu dijametralno su se razišla sa gledištima njegovih protivnika. Joanović je došao na fakultet da podučava studente, a ne da se preko njega dočepa titula, visokih honorara, procenata iz beogradskih sanatorijuma i svih ostalih političkih i drugih koristi koje jedan umešan čovek može iz tih titula izvući." Napisani članak naišao je na osudu i protivljenje mnogih intelektualaca tadašnjeg doba, studenata, ali i kod običnih ljudi.

Docent opšte patologije i patološke anatomije Univerziteta u Beogradu, doktor Dimitrije Tihomirov napisao je članak u časopisu "Glasnik za staleška i zdravstvena pitanja" 15.02.1932. godine, i odao počast doktoru Joanoviću: "S' osjećajima teškog i dubokog bola uslijed sasvim iznenadnog ogromnog i nikad nenadoknadivog gubitka za Medicinski Fakultet i za Kraljevinu Jugoslaviju pokušat ću da dadem tek blijedu sliku i kratku karakteristiku pokojnog učitelja a istovremeno jugoslavenskog pa i evropskog velikana-učenjaka." Koliko je profesor Joanović bio cenjen, kao naučnik, u inostranstvu, vidi se iz pisma, kojim je Međunarodni Ofis za javnu higijenu u Parizu izrazio saučešće gospodinu Ministru Socijalne Politike i Narodnog Zdravlja u njemu je rečeno sledeće: „Vest o smrti gospodina profesora Joanovića kod nas je izazvala jak bol, jer je on bio među najjače cenjenim učenjacima, a u svojim izlaganjima bio je najrađe slušan, i ako je lično bio veoma skroman".

Danas, ipak ostaju samo reči divljenja i poštovanja prema našem velikom naučniku i čoveku. Farmaceut Stevan Vukov iz Zrenjanina koji proučava život i delo profesora doktora Đorđa Joanovića na ovu temu izjavio je sledeće: "Jedno vreme sam bio bliži zaključku da je doktor Joanović bio žrtva zločina, nego da je izvršio samoubistvo. One koji sebi oduzmu život Crkva lišava opela, a profesor je bio shranjen u prisustvu sveštenika, po svim običajima srpske Pravoslavne crkve. Vremenom, saznajući više o Joanovićevom plemenitom karakteru i visokim moralnim načelima, postala mi je bliskija misao da je život ipak okončao samoubistvom, kao činom moralne superiornosti i nepristajanja na kompromise koji su bili u suprotnosti sa njegovim načelima. " - novine "Politika" 11. maja 2020. godine. Nakon smri profesora doktora Đorđa Joanovića osnovan je "Fond" pod njegovim imenom, za najbolje godišnje temate iz eksperimentalne patologije.

Povodom obeležavanja Osamdeset godina borbe protiv raka u Srbiji 10. decembra 2007. godine, profesor doktor Đorđe Joanović je posthumno odlikovan Zlatnom medaljom Srpskog društva za borbu protiv raka. Medalja je uručena akademiku V. Kanjuhu.

## NAUČNI RADOVI PROFESORA DOKTORA ĐORĐA JOANOVIĆA

Doprinos profesora doktora Đorđa Joanovića razvoju medicine, a pogotovo onkologije u Srbiji je od nemerljivog značaja. Naučni rad profesora doktora Đorđa Joanovića u domenu eksperimentalne patologije i imunopatologije bio je pionirski i u svetskim razmerama, tako da je imao impresivnu svetsku reputaciju. Napisao je 58 značajnih naučnih radova, sarađivao je sa dva najuglednija Medicinska Časopisa u Evropi. Naravno, osnova njegovog rada bila je postavljena već u Beču. Posvetio se eksperimentima kod onkoloških oboljevanja i izučavao epidemiologiju karcinogeneze. Sa naročitim se zanimanjem profesor Đorđe Joanović bavio studijama o patološkim promenama tkiva kod različitih oboljenja, uvek pri tome poklanjajući veliku i osobitu pažnju patološkoj anatomiji i histologiji. Današnju Bečku školu moderne patologije stvorio je profesor doktor Rihard Paltauf

such a massive and solemn procession to the railway station for a funeral. Several hundred students, mainly from the Medical Faculty, attended the burial, along with many prominent figures from the public life of the Kingdom of Yugoslavia. Dr. Joanović was interred at Beodra Cemetery on January 29, 1932. Although his death was suspected to be a suicide, Serbian Patriarch Varnava authorized a funeral service for the esteemed deceased.

On February 28, 1932, a politically motivated article titled “The Case of Professor Joanović” was published by his opponents, Dr. Svetozar Moačanin and Dr. Dušan Petrović, claiming: "He came to Serbia to create, and therefore his principled views on the faculty morally and scientifically diverged diametrically from those of his opponents. Joanović came to teach students, not to seek titles, high salaries, or benefits from Belgrade sanatoriums and other political or financial advantages."

The article was met with condemnation from many contemporary intellectuals, students, and ordinary citizens. Dr. Dimitrije Tihomirov, assistant professor of general pathology and pathological anatomy at the University of Belgrade, wrote in Glasnik za staleška i zdravstvena pitanja (February 15, 1932):

"With feelings of profound and deep sorrow over this sudden, immense, and irreparable loss for the Medical Faculty and the Kingdom of Yugoslavia, I will attempt to give but a faint picture and brief characterization of the late teacher, who was simultaneously a Yugoslav and European scholar of great stature." Dr. Joanović’s international reputation was evident from a letter of condolence from the International Office of Public Hygiene in Paris, addressed to the Minister of Social Policy and Public Health: "The news of Professor Joanović’s death has caused us deep sorrow, for he was among the most highly esteemed scholars, and in his lectures, he was always most attentively listened to, despite being personally very modest."

Today, only words of admiration and respect remain for this great scientist and human being. Pharmacist Stevan Vukov from Zrenjanin, who has studied Dr. Joanović’s life and work, commented: "For a time, I was closer to the conclusion that Dr. Joanović was the victim of a crime than that he committed suicide. Those who take their own lives are denied a church funeral, yet he was buried with a priest present, according to all Serbian Orthodox Church customs. Over time, understanding more about Joanović’s noble character and high moral principles, I became more inclined to believe that he ended his own life as an act of moral superiority, refusing to compromise his principles." — Politika, May 11, 2020.

After his death, a “Fund” was established in his name for the best annual topics in experimental pathology. On December 10, 2007, on the occasion of marking 80 years of the fight against cancer in Serbia, Professor Dr. Đorđe Joanović was posthumously awarded the Golden Medal of the Serbian Society for the Fight Against Cancer, presented to Academician V. Kanjuh..

## SCIENTIFIC CONTRIBUTIONS OF PROFESSOR DR. ĐORĐE JOANOVIĆ

*Contribution to Medicine and Oncology*

Professor Dr. Đorđe Joanović’s contribution to medicine, particularly oncology in Serbia, is immeasurable. His scientific work in experimental pathology and immunopathology was pioneering on a global scale, earning him an impressive international reputation. He authored 58 significant scientific papers and collaborated with two of the most prestigious medical journals in Europe. The foundation of his work had been laid during his time in Vienna. He devoted himself to experiments on oncological diseases and studied the epidemiology of carcinogenesis. Professor Joanović paid special attention to pathological changes in tissues caused by various diseases, with a particular focus on pathological anatomy and histology.

The modern Vienna school of pathology was developed by Professor Richard Paltauf together with his closest collaborators, Professor Karl Stanberg and Professor Đorđe Joanović. Joanović’s first scientific paper, published in 1899, addressed the origin and significance of plasma cells during pathological processes. From this early work, he turned to oncology, then a relatively new field, and began conducting experiments in advanced Viennese laboratories on oncological pathology.

*Work in Experimental Oncology and Oncological Pathology*

Dr. Đorđe Joanović was the first Serbian oncologist-scientist, starting his work in

zajedno sa svojim najbližim saradnicima profesorom doktorom Karlom Stanbergom i profesorom doktorom Đorđem Joanovićem. Prvi njegov stručni rad objavljen je 1899. godine i u njemu se bavio poreklom i značajem plazmičnih ćelija tokom patoloških procesa. Već prvi naučni rad doktora Đorđa Joanovića iz 1899. godine bio je zapažen. Ubrzo se opredelio za onkologiju kao tada novu oblast u medicini i počeo u naprednim bečkim laboratorijama da vrši eksperimente iz onkološke patologije.

*Rad na eksperimentalnoj onkologiji i onkološkoj patologiji*

Doktor Đorđe Joanović je bio prvi srpski onkolog-naučnik. On je počeo da radi na onkologiji 1920. godine. U njegovo vreme, zahvaljujući berlinskom patologu i profesoru Rudolfu Virhovu (1821.-1902. godine), već su prepoznati početni osnovni podaci o onkološkoj patologiji.

Profesor doktor Đorđe Joanović posvećivao je uvek veliko zanimanje za proučavanje raka, a naročite studije posvetio je pitanjima upliva na rastenje eksperimentalnih karcinoma i sarkoma, i to: načinom ishrane, hronične anemije, raznih alkaloida i ekstirpacije endokrinih žlezda. Verovao je da su dispozicija, lokalne promene i opšti metabolički poremećaj važni za razvoj raka. Profesor doktor Đorđe Joanović je istraživao patološku morfologiju nekih tumora, odnosno, bronhogenog karcinoma, cističnih tumora vrata, kalcifikacija i osifikacija atheroma, razvoj tumora iritacijom, multicentrično poreklo tumora u nekom organu i drugo. Istraživao je rast tumora in vivo i in vitro na kulturama tumorskog tkiva. Profesor Joanović je primetio da kastracija i splenektomija podstiču rast tumora; pirinač, takođe podstiču rast tumora, dok neke toksične supstance kao što su i male doze morfijuma, kokaina, ali i kinina intoksikacija toluilendijaminom usporavaju rast tumora. Imunološki aspekti terapije karcinoma korišćenjem fermentativnih ekstrakata tumorskog tkiva istih pacijenata prikazani su u radovima. Limfektazija, akumulacija plazmocita i proliferacija vezivnog tkiva sa sekvestracijom ćelija karcinoma ukazivali su na izlečenje od raka kod eksperimentalnih životinja. Uzimajući u obzir da infekcija erizipelom može uništiti karcinom kože, profesor doktor Đorđe Joannović je koristio pčelinji otrov u terapiji karcinoma. U doktorovim radovima dati su opsežni pregledi eksperimentalnih istraživanja raka i efekata radiotorijuma. Opšti osvrt doktora Joanovića na etiopatogenezu raka dao nam je relevantne i autentične podatke o stanju ovog problema u njegovo vreme.

*Rad na ekspererimentalnoj patologiji i patološkoj morfologiji*

Doktor Đorđe Joanović je rodonačelnik onkologije i utemeljivač eksperimentalne patologije u Srbiji. Profesor Joanović je takođe istraživao bojenje mikroorganizama u patološkim tkivima. Izučava patologiju jetre i piše značajne naučne studije iz te oblasti. Njegov rad na bolestima jetre pokrivao je različite aspekte, a njegov rad o patogenezi ikterusa nagrađen je od Belgijske kraljevske medicinske akademije.

Eksperimentalni radovi doktora Đorđa Joanovića o ikterusu, u kojima je uspeo da dokaže, da ikterus izazvan toluilendiaminom iščezava posle ekstirpacije slezene, poslužili su kao osnova za terapeutsku primenu ekstirpacije slezine kod hemolitičkih ikterusa. Od velikog su interesa eksperimentalne studije doktora Joanovića o jetri i metabolizmu masti. Radovi doktora Đorđa Joanovića iz eksperimentalne patologije i patološke morfologije odnose se na različite oblasti kao što su profilaksa tetanusa i anafilaktičkog šoka, problemi transplantacije i patologija ishrane.

*Otkrića o autoagresiji*

Profesor doktor Đorđe Joanović je primetio da su vojnici sa zalečenim povredama glave i mozga od vatrenog oružja ponekad imali jake glavobolje i umirali. Obdukcija ovakvih pacijenata pokazala je višestruke površine omekšanog moždanog tkiva, kako u blizini tako i na većoj udaljenosti od zarasle povrede mozga. Iste rezultate dobio je u svojim eksperimentima na belim pacovima koji su bili podvrgnuti mehaničkim povredama glave. Iz ovakvih zapažanja ljudi i životinja izveo je zaključak da produkti raspadanja mozga stimulišu naš imuni sistem da stvara antitela protiv njih, ali i protiv takvih supstanci u zdravim moždanim ćelijama, što izaziva višestruko omekšavanje mozga. Ovaj originalni etiopatogenetski koncept nekih bolesti pokušao je da primeni u terapiji površinskog karcinoma kože i tuberkuloznih granuloma životinja, ubrizgavajući dezintegracioni karcinom ili granulomsko tkivo (ili digestirani Koch bacili) pod kožu istih ljudi ili

oncology in 1920. At that time, thanks to the Berlin pathologist Rudolf Virchow (1821–1902), the basic principles of oncological pathology were already recognized.

Professor Joanović focused extensively on the study of cancer, especially on factors influencing the growth of experimental carcinomas and sarcomas, including: diet, chronic anemia, various alkaloids, and extirpation of endocrine glands. He believed that predisposition, local changes, and general metabolic disturbances were critical in cancer development.

He investigated the pathological morphology of tumors, including bronchogenic carcinoma, cystic neck tumors, atheroma calcification and ossification, tumor development through irritation, and the multicentric origin of tumors within an organ. He studied tumor growth in vivo and in vitro using tumor tissue cultures.

Professor Joanović observed that castration and splenectomy promoted tumor growth, while rice also stimulated growth. Certain toxic substances, including small doses of morphine, cocaine, and quinine, as well as toluidinediamine intoxication, slowed tumor growth. He explored the immunological aspects of cancer therapy using fermentative extracts from tumor tissues of the same patients. Lymphectasia, plasma cell accumulation, and connective tissue proliferation with sequestration of carcinoma cells were indicative of tumor regression in experimental animals.

Considering that erysipelas infection could destroy skin carcinoma, he also experimented with bee venom in cancer therapy. His publications provide extensive reviews of experimental cancer research and the effects of radium. Dr. Joanović's overall insight into cancer etiology and pathogenesis offered authentic and relevant information about the state of oncology in his era.

***Work in Experimental Pathology and Pathological Morphology***

Dr. Đorđe Joanović is regarded as the founder of oncology and experimental pathology in Serbia. He also researched staining of microorganisms in pathological tissues, studied liver pathology, and authored significant scientific papers in this area. His work on liver disease included studies on the pathogenesis of jaundice, recognized by the Belgian Royal Medical Academy.

His experimental studies demonstrated that jaundice induced by toluidinediamine disappeared after splenectomy, providing a foundation for therapeutic splenectomy in hemolytic jaundice. Of particular interest are his experimental studies on the liver and fat metabolism. Dr. Joanović's work in experimental pathology and pathological morphology covered various areas, including tetanus prophylaxis, anaphylactic shock, transplantation problems, and nutritional pathology. His scientific contributions laid the groundwork for modern pathology and oncology in Serbia and earned him international recognition as a pioneering researcher.

***Discoveries on Autoimmunity and Final Assessment of Professor Dr. Đorđe Joanović***

Discoveries on Autoaggression (Autoimmunity)

Professor Dr. Đorđe Joanović observed that soldiers with healed head and brain injuries from firearms sometimes suffered severe headaches and even died. Autopsies revealed multiple areas of softened brain tissue both near and distant from the healed injury site. Similar results were obtained in his experiments on white rats subjected to mechanical head injuries.

From these observations in humans and animals, he concluded that brain degradation products stimulate the immune system to produce antibodies not only against these products but also against similar substances in healthy brain cells, leading to widespread brain softening.

Joanović attempted to apply this original etiopathogenetic concept to therapy for superficial skin carcinoma and tuberculous granulomas in animals by injecting disintegrated carcinoma or granulomatous tissue (or digested Koch bacilli) under the skin of the same subjects. He also treated dermatoses, such as Trichophiton tonsurans infections, using disassociated products, and psoriasis using scarammas (scrapings). This method of treatment using coagulation products was successfully applied in psoriasis therapy. He presented these findings at the International Office for Hygiene in Paris in 1929, after which

eksperimentalnih životinja. Doktor Đorđe Joanović je takođe je lečio dermatoze: Trichophiton tonsurans svojim disociranim produktima kao i psorijazu svojim skrammama. Ovu je metodu lečenja produktima koagulacije doktor Joanović sa uspehom primenio i kod ječenja psorijaze. Uspeh ove metode lečenja profesor Joanović je izložio na sastanku Međunarodnog Ofisa za higijenu u Parizu 1929. godine, iza čega se na Institutu za patologiju još više počelo raditi s tom metodom. Profesor doktor Đorđe Joanović je bio pionir u otkrivanju procesa autoagresije u medicine. Otkriće autoagresije je najvažnije naučno dostignuće profesora doktora Đorđa Joanovića, ali malo poznata činjenica u inostranstvu i u Srbiji. Svoje otkriće saopštio je 1920. godine pred Bečkim lekarskim društvom i iste godine objavio dva rada u Bečkoj klinici Vochenschrift u Beču rad pod naslovom: " Efekat mozga i bakterijskih produkata dobijenih enzimskom destrukcijom " i rad pod nazivom: "Novi pogledi na poreklo i terapiju određenih bolesti".

Svojim rezultatima u eksperimentalnoj onkologiji i otkrićem koncepta autoagresije u medicine doktor Đorđe Joanović je stekao reputaciju jednog od najznačajnijih naučnika u svetskim razmerama. Belgijska Kraljevska akademija neuka dodelila mu je 1903. godine nagradu za njegov naučni rad.

Osim toga je profesor Joanović eksperimentalno radio na proučavanju tuberkuloze, upliva radioaktivnih supstancija na patološke promjene u organima, a bavio se i proučavanjem metode neoperativnog lečenja katarakte.

## ZAKLJUČAK

Profesor doktor Đorđe Joanović je čitav niz godina bio šef Instituta patološko-anatomske opšte poliklinike u Beču. Sa potpunim je pravom profesor Joanović uživao glas odličnog iskusnog specijaliste u patološko-anatomskoj dijagnostici, kao autoritet ogromnog poverenja i ugleda. Doprinos profesora doktora Đorđa Joanovića razvoju medicine, a pogotovo onkologije u Srbiji je od nemerljivog značaja. Naučni rad profesora doktora Đorđa Joanovića u domenu eksperimentalne patologije i imunopatologije bio je pionirski i u svetskim razmerama, tako da je imao impresivnu svetsku reputaciju. Naučni autoritet profesora Joanovića bio je tako velik, jer je podjednako vladao i morfološkim i fiziopatološkim delom svoje struke. Imao je retku osobinu veoma oštrog posmatrača i zato je brzo dolazio do uvek pravilnog zaključka. Profesor Joanović je nesebično čitav svoj život podredio nauci, te je čitav dan provodio na Institutu za patologiju. Uvek pristupačan i neobično pažljiv prema svakome, doktor Đorđe Joanović u svakom obraćanju studentima uvek im je pružao primer očinske ljubavi i susretljivosti, uvek objašnjavajući im njihove nedostatke, a u teškim prilikama podržavajući ih celim svojim autoritetom, a neretko i materijalno. Nastavu je profesor Joanović vodio, računao i zamišljao ne samo u školskim predavanjima i vežbama, nego je svaku čak i najmanju priliku pri dodiru sa mlađima iskorišćavao u tu svrhu, što je davao svima primer visoko džentlmenskog ponašanja, dubokog poverenja i predusretljivosti. Pri radu profesor Joanović pre svega tražio je od svih bez izuzetka zajedničko poverenje i saglasnost. Kao čovek, doktor Đorđe Joanović bio je uvek pristupačan za svakog studenta, lekara i svakog građanina. Njegovu dobrotu poznavao je svako, tko je bar jedanput sa njim imao razgovor ili tražio od njega kakav savet.

Profesor doktor Joanović bio je ne samo velik naučnik, nego i čovek otmeno visokih moralnih osobina. Svojom impozantnom spoljašnošću i uvek mirnim ponašanjem pravio je utisak neobično mirnog, staloženog a u isto doba i raspoloženog čoveka. Doktor Joanović bio je uvek otvoren, častan, plemenitog karaktera i visokih moralnih načela. Ne pristajanjem na kompromise koji su bili u suprotnosti sa njegovim načelima pokazao je čin moralne superiornosti. Profesor Đorđe Joanović bio je čovek retkih vrlina, sav sazdan od želje da sebe nesebično pokloni ne samo nauci i medicinskoj praksi nego i dostojanstvu naroda iz kojeg je potekao i kome je bio odan kao veliki patriota.

**Slika 4.** Osnovna škola "Đorđe Joanović" Novo Miloševo, Beodrad

his institute further developed work using this approach.

Professor Joanović was a pioneer in identifying autoaggression processes in medicine. This discovery of autoaggression represents one of his most important scientific achievements, though it remains little known both in Serbia and abroad. He first presented his findings in 1920 before the Vienna Medical Society and published two papers that year in the Viennese clinical journal Vochenschrift: "Effect of Brain and Bacterial Products Obtained by Enzymatic Destruction", "New Views on the Origin and Therapy of Certain Diseases". Through his results in experimental oncology and the discovery of autoaggression in medicine, Dr. Joanović gained a reputation as one of the most significant scientists internationally. In recognition, the Belgian Royal Academy awarded him a prize in 1903 for his scientific work.

Additionally, Professor Joanović conducted experimental studies on tuberculosis, the effects of radioactive substances on pathological organ changes, and non-surgical treatment methods for cataracts.

## CONCLUSION

Professor Dr. Đorđe Joanović served for many years as head of the Institute of General Pathological Anatomy in Vienna. He was widely recognized as an exceptionally skilled specialist in pathological-anatomical diagnostics, a figure of great authority, trust, and esteem.

His contributions to medicine and especially oncology in Serbia are of immeasurable significance. His work in experimental pathology and immunopathology was pioneering even by global standards, earning him an impressive international reputation. Joanović possessed equal mastery of both the morphological and physiopathological aspects of his discipline, combined with a rare ability for acute observation, enabling him to reach correct conclusions quickly.

Professor Joanović devoted his entire life selflessly to science, spending full days at the Institute of Pathology. He was always approachable, remarkably attentive, and treated his students with fatherly care, explaining their errors patiently and supporting them, both morally and sometimes materially. His teaching extended beyond lectures and exercises; he used every opportunity to instruct and guide younger generations, exemplifying gentlemanly conduct, deep trust, and responsiveness.

In his interactions, Joanović demanded mutual trust and consensus. He was accessible to all students, physicians, and citizens. His kindness was well known to anyone who spoke with him or sought his counsel.

Professor Dr. Joanović was not only a great scientist but also a man of noble moral character. His imposing presence, calm demeanor, and composed behavior created the impression of a serene, steady, and approachable individual. By refusing to compromise on principles contrary to his values, he demonstrated moral superiority.

He was a man of rare virtues, devoted entirely to science, medical practice, and the dignity of his nation. A true patriot, he dedicated himself to the advancement of knowledge, the care of patients, and the service of his country, leaving a legacy of scientific brilliance and human nobility..

**Figure 4.** Primary School "Đorđe Joanović" Novo Miloševo, Beodrad

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## TYPES AND SCOPE OF MANUSCRIPTS

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**Originalni rad** je sistematski obavljeno istraživanje nekog problema prema naučnim kriterijumima i jasnim ciljem istraživanja. Dužina teksta je ograničena na 3500 reči, maksimalno 5 tabela, grafikona, ili slika (do 12 stranica teksta).

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**Člancima iz istorije medicine** i zdravstvene kulture rasvetljavaju se određeni aspekti medicinske prakse u prošlosti. Dužina teksta može biti do 2500 reči (6 stranica).

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Organizacija kao autor:
WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Efect of brestfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000; 355: 451–5.
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Coffe drinking and cancer of the pancreas [editorial]. BMJ. 1981; 283: 628.
Volumen sa suplementom:
Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig heart anaphylaxis. Pharmacol Res Commun. 1988; 20 Suppl 5: 75–8.

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Autor je osoba(e):
Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.
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Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.
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Show the **results** (with the subtitle of the same name in BOLD) clearly and concisely. You should not display the same data both in tables and charts.

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**Journal articles**

Standard journal article:

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Organization as author:

WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000; 355: 451–5.

No authors listed:
Coffe drinking and cancer of the pancreas [editorial]. BMJ. 1981; 283 628.

A volume with a supplement:
Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig heart anaphylaxis. Pharmacol Res Commun. 1988; 20 Suppl 5: 75–8.

Books and other monographs

The author is a person (s):
Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.

Editor (s) as authors:
Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

Chapter in a book:
Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. Equalities and inequalities in health. 2nd ed. London: Academic Press; 1976. p. 165–78.

Meeting announcements: Harris AH, editor. Economics and Health: 1997: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia. Kensington, N.S.W.: School of Health Services Management, University of New South Wales; 1998.

Conference Articles:
Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, editors. Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society; 1987. p. 190-6.

Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. Equalities and inequalities in health. 2nd ed. London: Academic Press; 1976. p. 165–78.
Saopštenja sa sastanaka:
Harris AH, editor. Economics and health: 1997: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia. Kensington, N.S.W.: School of Health Services Management, University of New South Wales; 1998.
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Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, editors. Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society; 1987. p. 190-6.
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Cairns RB. Infrared spectroscopis studies of solid oxygen. Dissertation. Berkley, California: University of California, 1965.

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Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002;102(6). Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm
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Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15; 100 (10): 3828–31. Epub 2002 Jul 5.
CD-ROM:
Anderson SC, Poulsen KB. Anderson's electronic atlas of hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.
Monografija na internetu:
Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/.
Web lokacija:
Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.
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