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EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF HEMORRHAGIC FEVER WITH RENAL DISEASE SYNDROME IN THE AUTONOMOUS PROVINCE OF VOJVODINA

EPIDEMIOLOGIJA I KLINIČKE KARAKTERISTIKE HEMORAGIJSKE GROZNICE SA BUBREŽNIM SINDROMOM U AUTONOMNOJ POKRAJINI VOJVODINI

Vanja BOLJANOVIĆ[1], Dajana LENDAK[1,2], Mioljub RISTIĆ[2,3], Mirjana ŠTRBAC[3], Sandra STEFAN[1,2] and Danijela PRAŠTALO[1]

Summary

Introduction. The aim of this study was to determine the epidemiological and clinical characteristics of hemorrhagic fever with renal syndrome in Vojvodina from 2008-2015 and to examine the factors associated with acute renal failure and hemorrhagic syndrome. **Material and Methods.** Data were extracted from medical records spanning 2008 to 2015, including demographic, epidemiological, clinical, and laboratory findings at hospital admission, as well as the course and outcome of treatment. The study investigated the correlation between disease incidence and climate, focusing on acute renal failure, its risk factors, the incidence of hemorrhagic syndrome, and factors influencing hospital stay duration. **Results.** The highest incidence for hemorrhagic fever with renal syndrome was recorded in 2014, with a rate of 0.5 per 100.000 inhabitants. Acute renal failure was observed in 40% of patients, while mild manifestations of hemorrhagic syndrome were noted in 46.7% of cases. Factors contributing to acute renal failure included lumbar pain (p=0.005), creatinine concentrations (p=0.011), and Simplified Acute Physiology score (p=0.013). The average length of hospitalization was 10 days (range 7-13 days) and was correlated with increased leukocytosis (p=0.028; ρ=0.566), higher C-reactive protein values (p=0.014; ρ=0.686), lower serum sodium levels (p=0.009; ρ=0.772), higher serum creatinine concentrations (p=0.002; ρ=0.742), the Sequential Organ Failure Assessment score (p=0.013; ρ=0.612) and the Simplified Acute Physiology score (p=0.023; ρ=0.582). **Conclusion.** Climatic factors are associated with the incidence of hemorrhagic fever with renal syndrome. The overall outcome of the disease was favorable.

Key words: Hemorrhagic Fever with Renal Syndrome; Epidemiology; Incidence; Signs and Symptoms; Risk Factors; Renal Insufficiency; Climate; Treatment Outcome

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Sažetak

Uvod. Ciljevi istraživanja su utvrđivanje epidemioloških i kliničkih karakteristika hemoragijske groznice sa bubrežnim sindromom u Vojvodini, 2008−2015. godine i faktora povezanih sa razvojem akutne bubrežne insuficijencije i hemoragijskog sindroma. **Materijal i metode.** Podaci su uzeti iz istorija bolesti (2008−2015): demografski, epidemiološki, klinički i laboratorijski nalazi pri prijemu u bolnicu, tok i ishod lečenja. Ispitana je povezanost incidencije bolesti sa klimatskim uslovima; incidencija pojave akutne bubrežne insuficijencije, faktori rizika za njen nastanak, incidencija pojave hemoragijskog sindroma i faktori povezani sa dužinom hospitalizacije. **Rezultati.** Stope incidencije hemoragijske groznice sa bubrežnim sindromom su u porastu u Vojvodini; najviša incidencija je zabeležena 2014. godine (0,5/100.000 stanovnika). Iste godine zabeležen je porast količine padavina, više prosečne temperature vazduha zimi i veća vlažnost vazduha. Razvoj akutne bubrežne insuficijencije zabeležen je kod 40%, blage manifestacije hemoragijskog sindroma kod 46,7% bolesnika. Faktori rizika za nastanak akutne bubrežne insuficijencije su: bol u lumbalnim ložama (p = 0,005), koncentracija kreatinina (p = 0,011) i *Simplified Acute Physiology score* (p = 0,013). Prosečna dužina hospitalizacije iznosila je 10 (7−13) dana i korelirala je sa: izraženijom leukocitozom (p = 0,028; ρ = 0,566), višim vrednostima C-reaktivnog proteina (p = 0,014; ρ = 0,686), nižim koncentracijama natrijuma (p = 0,009; ρ = 0,772) i višim koncentracijama kreatinina u serumu (p = 0,022; ρ = 0,585). **Zaključak.** Klimatski faktori povezani su sa incidencijom hemoragijske groznice sa bubrežnim sindromom. Klinička slika je bila blaga, sa povoljnim ishodom.

Ključne reči: hemoragijska groznica sa bubrežnim sindromom; epidemiologija; incidenca; znaci i simptomi; faktori rizika; bubrežna insuficijencija; klima; ishod lečenja

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Abbreviations

HFRS	– Hemorrhagic fever with renal syndrome
ARI	– Acute renal injury
AKIN	– Acute Kidney Injury Network
SOFA	– Sequential Organ Failure Assessment
SAPS II score	– Simplified Acute Physiology Score
CRP	– C-reactive protein
ALT	– Alanine aminotransferase
AST	– Aspartate aminotransferase
Aptt	– Activated partial thromboplastin time
APV	– Autonomous province of Vojvodina
PUUV	– Puumala virus

Introduction

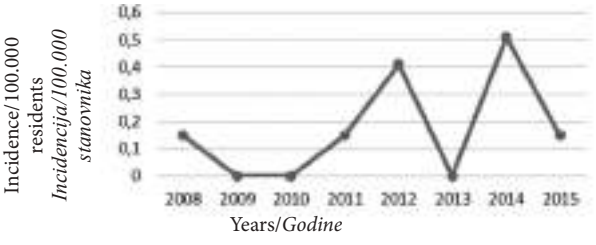
Hemorrhagic fever with renal syndrome (HFRS), caused by the Hantaan virus, is a zoonosis disease with a global distribution, posing significant challenges to public health worldwide [1–3]. Key factors affecting the virus's viability outside the host include temperature, humidity, exposure to ultraviolet light and sunlight, and the organic composition of the contaminated fluid. The optimal environmental conditions for virus survival can vary among different strains of the Hantaan virus, contributing to the distinct infection dynamics observed in both rodents and humans [4–6].

Material and Methods

This study adheres to established scientific methodologies in medical research, having obtained approval from the University Clinical Center Clinical Etics Committee (No. 6, 00-53). Conducted as a retrospective observational study, data were sourced from the medical records of patients admitted to the Infectious Diseases Clinic at the Clinical Center of Vojvodina. Additionally, epidemiological data regarding HFRS in the Autonomous Province (AP) of Vojvodina were retrieved from the annual publication "Infectious Diseases in AP Vojvodina", published by the Disease Control and Prevention Center of the Institute for Public Health of Vojvodina in collaboration with healthcare centers across the region. The data sources included disease histories and infectious disease surveillance. HFRS supervision in our region is conducted through passive collection of reports on documented cases and mortality. We employed a descriptive epidemiological methodology, analyzing registered HFRS cases chronologically and demographically. The results, including an analysis of the association between climatic factors and disease frequency as well as the clinical characteristics of the illness, are presented in both tabular and graphical formats. Standard epidemiological and clinical indicators, such as percentages, incidence rates, median, interquartile ranges, and correlation coefficients were utilized. The study covered eight consecutive years from 2008 to 2015. Eligibility criteria included individuals with suspected HFRS, characterized by a sudden onset of illness in those who had either traveled to HFRS-endemic regions or had contact with rodent excreta within two months prior to symptom onset. The illness had to manifest with at least two of the following clinical features: tremors, chills, headache, back pain, bleeding, hypotension, abdominal pain, and acute renal failure. Confirmation of HFRS required meeting at least one laboratory criterion: a positive result for Hantaan virus-specific IgM or a fourfold increase in the titer of Hantaan virus-specific IgG. For the clinical component of the research, data were gathered from medical records including patient age, gender, symptoms reported at the time of hospital admission, duration of symptoms prior to admission, and initial laboratory parameters recorded at admission. These parameters comprised a complete blood count, concentrations of C-reactive protein, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, urinalysis findings, and calculated Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score (SAPS II score) [7]. Patients were monitored throughout hospitalization, documenting the occurrence of hemorrhagic syndrome, the highest recorded creatinine values, the development of acute renal failure as defined by the Acute Kidney Injury Network (AKIN), disease outcomes, and length of hospital stay [8]. According to AKIN criteria, acute renal failure is defined by an increase in serum creatinine of at least 26 μmol/L or more than 150% of baseline values, or urine output less than 0.5 ml/kg of body weight over 6-12 hours. Statistical data were processed using SPSS version 23.0. Results for categorical variables are presented as total number (n) and percentage (%), with differences between groups assessed using the chi-square (χ^2) test. Continuous variables are reported as median and interquartile range, based on the Shapiro-Wilk test findings indicating statistically significant deviations from normal distribution for most variables. Differences between the two groups were compared using the Mann-Whitney U test. Spearman's rank correlation was used for correlation analysis, with statistical significance set at $p < 0.05$.

Results

According to epidemiological data, 28 cases of HFRS were documented within the specified period in patients from the Autonomous Province of Vojvodina (APV). Detailed information regarding the progression and outcome of the disease was accessible for 15 of these cases **(Table 1).**

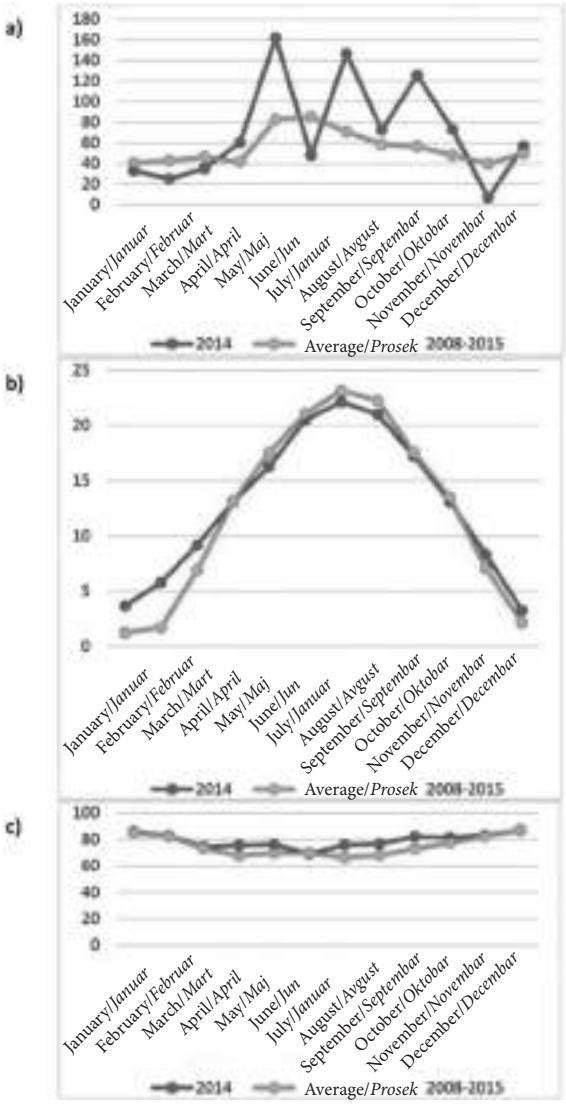


Graph 1. Chronological distribution of HFRS in the APV, from 2008 to 2015

Grafikon 1. *Hronološka distribucija HGBS u Autonomnoj pokrajini Vojvodini, 2008–2015. godine*

Table 1. Age and gender specific distribution of HFRS patients in the AP of Vojvodina in the period from 2008 to 2015
Tabela 1. *Uzrasno i rodno specifična distribucija obolelih od hemoragijske groznice sa bubrežnim sindromom u Autonomoj pokrajini Vojvodini u periodu od 2008. do 2015. godine*

	N/*Br.*	%
Age/*Uzrast*		
Under 20 years old/*Mlađi od 20 godina*	2	7.14
21-30	7	25.00
31-40	10	35.71
41-50	8	28.57
51-60	0	0.00
Over 60 years old/*Preko 60 godina*	1	3.57
Gender/*Pol*		
Male/*Muški*	26	92.90
Female/*Ženski*	2	7.10



Graph 2. Average monthly values of temperature, precipitation and air humidity in the AP of Vojvodina, from 2008 to 2015
Grafikon 2. *Prosečne mesečne vrednosti temperature, količine padavina i vlažnosti vazduha u AP Vojvodini, 2008–2015. godine*

The registered incidence rates of HFRS in the APV during the observed period ranged from 0.0 in 2009, 2010, and 2013, to 0.5 in 2014. An escalation in HFRS incidence was noted during severe flooding in Serbia in 2014 **(Graph 1).**

The average monthly values of temperature, precipitation, and air humidity in the APV from 2008 to 2015 are depicted in the graph.

In relation to the data depicted in **Graph 2**, it is evident that the most significant fluctuations occurred in the average values for rainfall. In May, July, and September, precipitation levels were recorded at twice the average amount for those respective months. Throughout 2014, higher relative air humidity values were observed compared to the average. Regarding air temperature, slightly elevated temperatures were noted during the winter months, while slightly lower temperatures were observed during the summer months, in comparison to the respective monthly averages.

Incidence of Acute Renal Injury (ARI) and clinical characteristics associated with its development in patients with HFRS

Initially elevated creatinine values were recorded in 4 patients (26.7%), while subsequent increases beyond the reference limits were observed in another 4 patients (26.7%), totaling 53.3% of patients with elevated creatinine levels. Six patients met the criteria for diagnosing ARI. Proteinuria was documented in 7 patients (46.7%), with 5 classified as mild (57.1%), 1 as moderate (14.3%), and 2 as severe (28.6%) proteinuria.

Tables 2 and 3 display pertinent data concerning hospital admission symptoms in patients with and without ARI, as well as age, duration of symptoms prior to hospitalization, time from admission to appropriate diagnosis, and predictive scores (SAPS II and SOFA score).

Table 4 presents the values of laboratory parameters recorded upon hospital admission, categorized by the presence of ARI.

The correlation analysis revealed statistically significant positive correlations between the highest

Table 2. Symptoms reported by patients at hospital admission, in the group with and without ARI
Tabela 2. *Simptomi koje su bolesnici prijavljivali pri prijemu u bolnicu, u grupi sa i bez ABI*

Symptoms *Simptomi*	Yes/No *Da/Ne*	ARI/*ABI* n (%)	Without ARI/*Bez ABI* n (%)	p/*p*
Fever/*Povišena telesna temperarura*	Yes/*Da*	6 (100%)	9 (100%)	–
Headache/*Glavobolja*	Yes/*Da*	5 (83%)	1 (11.1%)	0.475
Abdominal pain/*Abdominalni bol*	Yes/*Da*	1 (11.1%)	5 (83%)	0.475
Nausea, vomiting/*Muka, povraćanje*	Yes/*Da*	3 (50%)	3 (50%)	0.833
Lumbar pain/*Bol u lumbalnom delu leđa*	Yes/*Da*	5 (83.3%)	1 (11.1%)	0.005
Hemorrhagic syndrome/*Hemoragijski sindrom*	Yes/*Da*	0 (0%)	6 (100%)	0.389
Vision problems/*Problemi sa vidom*	Yes/*Da*	1 (11.1%)	5 (83%)	0.475
Diarrhea/*Dijareja*	Yes/*Da*	1 (11.1%)	5 (83%)	0.475

Table 3. Age, duration of complaints before admission, time from admission to suspicion of HFRS and predictive scores in patients who developed ARI compared to patients who did not develop ARI; Group of patients with and without acute renal failure in relation to symptoms recorded at hospital admission
Tabela 3. *Uzrast, dužina tegoba pre prijema, vreme proteklo od prijema do postavljanja sumnje na HGBS i prediktivni skorovi kod bolesnika kod kojih je došlo do razvoja ABI u odnosu na bolesnike kod kojih se ABI nije razvila; Grupa pacijenata sa i bez akutne bubrežne insuficijencije u odnosu na simptome zabeležene pri prijemu u bolnicu*

	ARI *ABI*	Median *Medijana*	Interquartile range *Interkvartilni raspon*	p/*p*
Age *Uzrast*	Without ARI/*Bez ABI* With ARI/*Sa ABI*	32.00 34.00	26.00-47.00 28.00-40.00	0.723
Duration of symptoms before admission *Trajanje tegoba pre prijema*	Without ARI/*Bez ABI* With ARI/*Sa ABI*	4.00 6.00	3.00-4.00 5.00-7.00	0.077
Time from admission to suspicion of HFRS *Vreme od prijema do postojanja sumnje na HGBS*	Without ARI/*Bez ABI* With ARI/*Sa ABI*	4.50 5.00	3.00-6.00 4.00-6.50	0.850
SOFA *SOFA*	Without ARI/*Bez ABI* With ARI/*Sa ABI*	2.00 3.50	0.00-2.00 2.00-6.00	0.101
SAPS II *SAPS II*	Without ARI/*Bez ABI* With ARI/*Sa ABI*	12.00 20.00	9.00-13.00 16.00-24.00	0.013

Table 4. Laboratory data in patients who developed ARI compared to the ones who did not develop ARI
Tabela 4. *Laboratorijski podaci kod bolesnika kod kojih je došlo do razvoja ABI u odnosu na bolesnike kod kojih se ABI nije razvila*

	ARI/*ABI*	Without ARI/*Bez ABI*	p/*p*
Leukocytes/*Leukociti* (x10^9/l)	10.05 (5.16-10.69)	8.70 (6.51-9.60)	0.724
Erythrocytes/*Eritrociti* (x10^9/l)	4.98 (4.73-5.57)	4.57 (4.52-5.02)	0.099
Platelets/*Trombociti* (x10^9/l)	70.75 (55.0-207.00)	74.00 (57.00-178.00)	0.906
Aptt a second/*Aptt sekunda*	0.97 (0.97-0.98)	2.89 (1.86-4.92)	0.564
Prothrombin time a second/*Protrombinsko vreme u sekundi*	7.15 (0.91-13.40)	1.11 (1.01-5.75)	0.767
CRP/*CRP* (mg/l)	59.15 (30.45-93.55)	54.85 (31.15-145.400)	0.865
Urea/*Urea* (mmol/L)	7.950 (5.80-15.00)	6.00 (5.00-6.30)	0.157
Serum creatinine/*Kreatinin u serumu* (µmol/L)	98.50 (90.0-253.00)	92.00 (92.0-98.00)	0.375
Highest recorded creatinine values *Najviše zabeležene vrednosti kreatinina* (µmol/L)	215.50 (140.0-402.00)	93.00 (92.0-117.00)	0.011
Sodium/*Natrijum* (mmol/L)	139.00 (136.0-140.00)	139.00 (138.0-141.00)	0.599
AST/*AST* (U/L)	44.50 (38.0-62.00)	26.00 (19.0-31.00)	0.077
ALT/*ALT* (U/L)	36.50 (31.0-48.00)	28.00 (19.0-41.00)	0.346

recorded creatinine values during hospitalization and:

– The duration of symptoms before admission to the hospital, of both the mean and high intensity (p=0.047; p=0.608), with the former being statistically significant.

– Leukocyte values, of moderate intensity (p=0.048; p=0.517).

– Initially recorded values of urea (p=0.002; p=0.742) and creatinine (p=0.05; p=0.685) of high intensity.

– The initially recorded values of predictive SOFA score (p=0.013; p=0.612) and SAPS II (p=0.023; p=0.582), of moderate to high intensity.

No statistically significant correlation was observed between the highest recorded creatinine values and other laboratory parameters (p>0.05).

Hemorrhagic syndrome, clinical and laboratory manifestations in HFRS patients

Thrombocytopenia was documented in 9 out of 15 patients (60%), prolonged prothrombin time in 2 out of 15 patients (13%), and manifestations of hemorrhagic syndrome, including epistaxis, microhematuria, skin hemorrhages, and gum bleeding, in 7 out of 15 patients (46.7%).

There was no statistically significant difference observed in gender or disease symptoms concerning the occurrence of hemorrhagic syndrome (p>0.05). Similarly, no statistically significant differences were noted in age, duration of complaints before hospital admission, predictive scores, or laboratory parameters between patients with and without hemorrhagic syndrome (p>0.05).

Hemorrhagic fever with renal syndrome - Duration of hospitalization and disease outcome among all subjects

The mean duration of hospitalization was 10 days (range 7-13).

None of the documented disease symptoms exhibited a statistically significant impact on the duration of hospitalizations (p>0.05).

Correlation analysis revealed associations between the duration of hospitalization and the following laboratory parameters:

– Leukocytosis exhibited a positive correlation of moderate intensity (p=0.028; ρ=0.566).

– CRP showed a positive correlation of moderate to high intensity (p=0.014; ρ=0.686).

– The highest recorded creatinine values demonstrated a positive correlation of moderate intensity (p=0.022; ρ=0.585).

– Serum sodium concentrations exhibited a negative correlation of high intensity (p=0.009; ρ= -0.772).

Discussion

Infectious diseases have historically emerged following major natural disasters, particularly after the flooding of river basins and acute food shortages caused by severe storms. As long as microorganisms persist, alongside their primary vectors and reservoirs among animals, this correlation will continue to exist [9, 10].

Hemorrhagic Fever with Renal Syndrome is endemic in the Balkan countries, with periodic outbreaks and sporadic cases. Annually, about 100 cases are reported in the Balkan Peninsula, with a noticeable seasonal distribution, showing higher prevalence during the summer months, with occupation being the predominant risk factor [11, 12]. Epidemiologically, it is well-established that extraordinary conditions such as floods, earthquakes, and wars facilitate the transmission of infectious diseases. However, a higher frequency of HFRS is observed in the AP of Vojvodina, despite its lack of direct exposure to these phenomena. In our study, the rise in the number of patients during specific years can be attributed to findings from mainland China, which demonstrated that increased rainfall, higher temperatures, and elevated air humidity are conducive to the survival and proliferation of the causative agent [11, 12]. This infection occurs more frequently in regions where the annual average temperature is around 20°C, the annual average relative humidity ranges between 50-80%, and the annual total precipitation ranges from 400 to 1600 mm. In contrast, no cases have been reported in western China, where the average altitude exceeds 2000 m, and precipitation is infrequent, resulting in relative humidity typically exceeding 50% and fewer than 60 rainy days per year. Based on the aforementioned data, most researchers believe that precipitation, coupled with lower air temperatures, are the most significant meteorological factors influencing the abundance and activity of rodents, the primary vector of the HFRS causative agent of [13–16]. The average duration of illness prior to hospitalization in our study was 5 days. Among the 15 patients with available data on laboratory parameters, disease course, and outcome, no fatalities were recorded. Different authors, employing diverse sample populations and diagnostic criteria for ARI, have identified different predictors for its etiology. In contrast to data from Asian regions, where high mortality rates are documented, in our country, all patients presented with a less severe clinical presentation, with no reported fatalities, and none necessitated hemodialysis among those who developed ARI. These findings align with global data suggesting that Puumala virus (PUUV) induces milder disease manifestations [17–19]. The objective of our study was to investigate factors associated with the occurrence of ARI and hemorrhagic manifestations, and to determine the primary determinants of hospitalization duration among patients with HFRS. ARI, a primary complication of HFRS, is a multifaceted disorder characterized by clinical manifestations ranging from a minimal elevation in serum creatinine levels to the requirement for hemodialysis [17, 24]. Recent epidemiological studies indicate considerable diversity in etiology and risk factors, and highlight the elevated mortality rates linked with this disease, particularly when dialysis

is required. These studies suggest an association with the subsequent development of HFRS and dependency on dialysis. Emerging evidence also suggests that even minor elevations in serum creatinine levels are correlated with increased patient mortality [8]. Utilizing the AKIN definition of ARI, our findings reveal that among the 15 patients with a confirmed diagnosis of HFRS, 6 developed ARI. Factors associated with elevated creatinine levels and the development of ARI during hospitalization included the initially recorded values of urea and creatinine, the duration of symptoms before hospital admission, SAPS II score, and leukocytosis upon hospital admission [7].

In one of the numerous studies on HFRS conducted in China, the SAPS II score was positively correlated with mortality in ARI cases. Conversely, SOFA score, widely used for assessing hospitalization duration, mortality risk, and as a major prognostic indicator for severe sepsis, also showed significant correlation with the severity of HFRS. This suggests that these scoring systems possess strong predictive value for the progression of severe HFRS [8]. Our study also demonstrates a positive correlation between SAPS II score values and the occurrence of acute renal failure. While the findings for the SOFA score exhibit a clear trend towards statistical significance, we hypothesize that this was not reached due to the sample size limitations.

Regarding the development of hemorrhagic syndrome, data from various studies suggest diverse factors associated with the occurrence of hemorrhagic manifestations [20, 21].

Our study did not demonstrate a difference in the presentation of specific symptoms/signs or laboratory findings between patients with and without hemorrhagic manifestations. This observation may be explained by the mild nature of the hemorrhagic manifestations observed in our patients, which were limited to isolated instances of epistaxis, microhematuria, and skin and gum bleeding. In contrast, more pronounced hemorrhagic manifestations are documented in endemic regions with other virus subtypes. Another explanation could be the small sample size, which may be insufficient to detect statistically significant differences.

Our results indicate that the average duration of hospitalization was 10 days (range 7-13), and none of the symptoms significantly influenced the length of hospital stay. However, the duration of hospitalization was associated with leukocytosis, CRP values, highest creatinine values, and serum sodium concentration. Consistent with our findings, a study conducted in Slovenia reported an average hospital stay of 10.4 days [22, 23].

Conclusion

In our study, the clinical presentation of hemorrhagic fever with renal syndrome was predominantly mild among most patients, with acute renal failure observed in 40% of cases, none of which required hemodialysis. The peak incidence of the disease occurred in 2014, coinciding with a significant rise in precipitation levels, slightly elevated average air temperatures in winter, lower temperatures in summer months, and increased air humidity. Further detailed investigation into environmental conditions, as well as other contributing factors, is warranted to better understand the rise in the number of patients with hemorrhagic fever with renal syndrome.

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PREDICTOR ANALYSIS OF SMELL AND TASTE LOSS ONSET AND ITS SIGNIFICANCE IN COVID-19 DISEASE

ANALIZA PREDIKTORA ZA NASTANAK SIMPTOMA GUBITKA ČULA MIRISA I UKUSA I NJIHOV ZNAČAJ KOD COVID-19 BOLESTI

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Summary

Introduction. COVID-19 is defined as an infectious disease caused by the coronavirus. It manifests with various symptoms, including the loss of smell and taste. While the exact pathogenesis remains unclear, it is believed that these symptoms occur due to the virus's impact on angiotensin receptors. Post-COVID syndrome, which includes various long-term symptoms, can develop after the initial illness. This study aimed to identify predictors of taste and smell loss during COVID-19, evaluate their prognostic significance for disease outcomes, and explore their connection to the respondents' constitutional characteristics. **Material and Methods.** The research was conducted using an online questionnaire completed 194 respondents who had recovered from COVID-19 disease (150 experienced taste and/or smell loss, and 44 did not). In January and February 2022, two versions of the questionnaire were distributed based on the presence or absence of these symptoms. **Results.** Significant predictors of sensory loss include profession requiring interaction with people, non-smoking status, absence of allergies, and experiencing mild respiratory infection more than once a year. The presence of sensory loss does not necessarily indicate a milder clinical course of the disease. Post-COVID symptoms (gastrointestinal, cardiovascular, skin lesions, and reactivation of herpes simplex virus) occurred significantly more often in the group that experienced taste and/or smell loss. **Conclusion.** While there are predictors for the development of taste and/or smell loss, they are not the guarantee a better disease outcome. Post-COVID syndrome can manifest differently across various groups of respondents.

Key words. COVID-19; Taste Disorders; Olfaction Disorders; Anosmia; Ageusia; Post-Acute COVID-19 Syndrome; Angiotensin-Converting Enzyme 2; Receptors, Angiotensin; Taste Buds; Surveys and Questionnaires

Sažetak

Uvod. COVID-19 se definiše kao infektivna bolest uzrokovana virusom korona. Bolest se manifestuje mnogobrojnim simptomima, među kojima se nalaze gubitak čula mirisa i/ili ukusa. Patogeneza nastanka ovih simptoma nije u potpunosti razjašnjena, ali se smatra da nastaju delovanjem virusa na angiotenzinske receptore, prisutne u sluznici respiratornog trakta i usne duplje. Nakon preležane bolesti, može se javiti i tzv. postkovid sindrom koji obuhvata različite dugotrajnije simptome. Cilj rada podrazumevao je određivanje prediktora za nastanak simptoma gubitka čula mirisa i ukusa u toku COVID-19 bolesti i analiziranje njihovog uticaja na ishod bolesti i njihovu povezanost sa konstitucionalnim obeležjima ispitanika. **Materijal i metode.** Istraživanje je sprovedeno putem online upitnika na ukupno 194 ispitanika koji su preležali COVID-19, od kojih je 150 imalo simptome gubitka čula mirisa i/ili ukusa, a 44 nije. Kreirane su dve verzije upitnika koje su dostavljane ispitanicima nakon prethodnog intervjuisanja o prisustvu ili odsustvu navedenih simptoma, tokom januara i februara 2022. godine. **Rezultati.** Značajni prediktori za nastanak gubitka čula su: profesija koja podrazumeva rad sa ljudima, nekonzumiranje cigareta, odsustvo alergija i prisustvo blage respiratorne infekcije više od jedanput godišnje. Prisustvo simptoma gubitka čula ne znači nužno i blažu kliničku sliku bolesti. Postkovid simptomi (gastrointestinalni, kardiovaskularni, kožne promene i reaktivacija herpes simpleks virusa), značajno češće su se javljali u grupi ispitanika koja je imala simptome gubitka čula mirisa i/ili ukusa. **Zaključak.** Postoje prediktori za nastanak simptoma gubitka čula mirisa i/ili ukusa, ali oni ne predstavljaju garanciju za povoljniji ishod bolesti. Postkovid sindrom može imati različite oblike kod različitih grupa ispitanika.

Ključne reči. COVID-19; poremećaji čula ukusa; poremećaji čula mirisa; anosmija; ageuzija; post-COVID sindrom; angiotenzin konvertujući enzim tip 2; angiotenzin receptori; kvržice na jeziku; ankete i upitnici

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Abbreviations

SARS-CoV-2 virus – Severe Acute Respiratory Syndrome Coronavirus 2
n-CoV – new strain of coronavirus
ACE2 receptors – angiotensin-converting enzyme 2 receptors

Introduction

COVID-19 is defined as an infectious disease caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus 2) [1]. At the end of 2019, a new strain of coronavirus (n-CoV) emerged in China, causing a systemic infection in humans. This strain had not been previously identified in humans. On February 11, 2020, the World Health Organization announced the official name of the disease as COVID-19, caused by the SARS-CoV-2 strain [2]. The clinical presentation of COVID-19 varies in severity. Common symptoms include weakness, malaise, fever, muscle and joint pain, cough, shortness of breath, nausea, vomiting, diarrhea, loss of appetite, headache, and a reduced or complete loss of the sense of smell and/or taste. Unlike other upper respiratory infections such as the flu or a cold, COVID-19 can independently cause a reduced sensation or even a complete loss of smell and/or taste. This specificity suggests a different pathogenesis for these symptoms. The primary mechanism of action for SARS-CoV-2 involves binding to angiotensin-converting enzyme 2 (ACE2) receptors. These receptors are widely distributed in the membranes of epithelial cells of the skin, oral mucosa, nasal cavity, and endothelial cells of blood vessels [3,4]. ACE2 converts angiotensin II into a fragment called Ang [1–7], which dilates blood vessels and lowers local blood pressure. When the virus binds to numerous ACE2 receptors, it stimulates and subsequently dysregulates them, leading to an increase in the local concentration of angiotensin II, which can cause significant increases in blood pressure and tissue inflammation. The high concentration of ACE2 receptors in the mucous membranes of the respiratory tract indicates that area is the primary site of action for the SARS-CoV-2 virus. This also explains the taste disorders observed in COVID-19 patients, as ACE2 receptors are significantly present in the epithelial cells of the tongue and salivary glands [5–7]. Post-COVID symptoms, which can manifest across various organ systems, are increasingly common. Neurological/cognitive symptoms include brain fog, dizziness, impaired attention, confusion, speech disorders, forgetfulness, tingling or loss of sensation in extremities, and burning skin sensations. Cardiovascular symptoms include chest pain, palpitations, and arrhythmias. Gastrointestinal symptoms include diarrhea, abdominal pain, bloating, nausea, vomiting, anorexia, and loss of appetite. Respiratory symptoms include chronic fatigue, shortness of breath, cough, sore throat, and a choking sensation. Musculoskeletal symptoms include pain in muscles, bones and joints, and joint stiffness. Psychological symptoms include emotional instability, anxiety, depression, and insomnia [8].

Material and Methods

This research was conducted as an epidemiologic retrospective cross-sectional study using a custom-developed questionnaire. The questionnaire was created based on a literature review and existing knowledge about COVID-19. Data collection occurred via an online questionnaire, which participants completed independently, and through direct surveys conducted by the researcher. The survey took place in January and February 2022, targeting respondents residing in the Republic of Serbia. The inclusion criterion was a history of COVID-19 infection between March 2020 and December 2021. The sample comprised individuals who had experienced COVID-19, reached through acquaintances and informal groups or social media profiles. There were no age restrictions. Participants were divided into two groups: one with symptoms of loss of smell and/or taste, and a control group of individuals who had COVID-19 but did not experience these symptoms.

Questionnaire 1 - respondents with symptoms of loss of smell and/or taste

This questionnaire consisted of five sections. Section 1 consisted of questions related to constitutional characteristics and predictors, including gender, age, current profession, allergies, cigarette consumption, and tendency to experience mild respiratory infections annually. Section 2 consisted of questions regarding previous COVID-19 disease, including time of illness (month and year), symptoms, hospitalization and, vaccination status. Section 3 consisted of questions regarding symptoms of loss of smell and/or taste, such as intensity, onset, and duration of these symptoms, treatment, and olfactory training. Section 4 consisted of questions regarding Post-COVID consequences, the symptoms experienced in the six months following the illness, and diagnoses received during the same period. The last section required a photograph of the dorsal surface of the tongue, with precise instructions to ensure usability for analysis, aimed at minimizing direct contact due to the current epidemiological situation.

Questionnaire 2 - respondents without symptoms of loss of smell and/or taste

Questionnaire 2 was similar to Questionnaire 1, except it lacked the section concerning symptoms of loss of smell and/or taste. This alignment was necessary to compare the two groups of respondents effectively.

Responses concerning symptoms experienced during COVID-19 were classified by severity into mild, moderate, and severe clinical presentation. They were also categorized by predominant symptom type: respiratory, neurological, or other. Post-COVID symptoms were similarly categorized. Photographs of the dorsal surface of the tongue were analyzed to determine its anatomical characteristics and the number of fungiform papillae, which transmit taste sensations. Properly captured images showed these papillae as

distinct red nodules, enabling analysis. Fungiform papillae were counted visually on the anterior third of the dorsal surface. Each tongue was segmented into anterior, middle and posterior thirds, and measured using a ruler against the visible length of the dorsal surface in each photo. Data analysis was performed using the SPSS 21 statistical software. Results were presented as absolute frequencies and mean values in tabular format. Descriptive statistical techniques were used for result depiction. The chi-square test and t-test were employed to determine statistically significant differences between groups, with significance set at $p<0.05$.

Results

The sample consisted of 194 respondents diagnosed with COVID-19. Of these, 150 exhibited symptoms of anosmia and/or ageusia during their illness, while 44 did not. Among the total respondents, 68 were male and 126 were female ($p<0.05$). Additionally, 150 respondents were employed in professions involving direct interaction with others, while 44 were not. The average age of the respondents was 33.97 years, with ages ranging from 11 to 81 years. Statistical analysis revealed a significantly higher proportion of females, individuals employed in people-centric professions, non-smokers, those without allergies, and those with recurrent mild respiratory infections among those experiencing symptoms of anosmia and/or ageusia during COVID-19 infection ($p<0.05$). However, the number of fungiform papillae in the anterior third of the tongue did not show a significant association with the occurrence of these symptoms. Conversely, among respondents without symptoms of anosmia and/or ageusia, significant predictors were professions involving interpersonal interactions and non-smoking status ($p<0.05$). Gender, presence of allergies, recurrent mild respiratory infections, and the number of fungiform papillae in the anterior tongue segment were not significant factors. The most prominent predictor distinguishing the two groups was the proportion of non-smokers ($p<0.05$) **(Table 1).**

In the cohort of respondents experiencing symptoms of sense loss, a moderate clinical presentation characterized predominantly by neurological symptoms was observed, with no requirement for hospitalization ($p<0.05$). Post-COVID symptoms, particularly respiratory and neurological manifestations, significantly prevailed in this group ($p<0.05$). Conversely, among subjects without symptoms of anosmia and/or ageusia, a moderate clinical presentation marked by predominantly neurological symptoms

Table 1. Analysis of predictor significance within and between the two groups
Tabela 1. *Analiza značaja prediktora unutar grupa i između dve grupe*

	Group 1: with sense loss *Grupa 1: sa gubitkom čula*	Total *Ukupno*	χ^2 test within Group 1 *χ^2 test u okviru grupe 1*	Group 2: without sense loss *Grupa 2: bez gubitka čula*	Total *Ukupno*	χ^2 test within Group 2/*χ^2 test u okviru grupe 2*	χ^2 test between the two groups *χ^2 test između dve grupe*
Male/*Muškarci*	48 (32%)	150	p>0.05	20 (45.4%)	44	p>0.05	χ^2=0.100
Female/*Žene*	102 (68%)	150	p<0.05	24 (54.5%)	44	p>0.05	p>0.05
Work with people *Rad sa ljudima*	114 (76%)	150	p<0.05	36 (81.8%)	44	p<0.05	χ^2=0.418
Work without people *Rad bez ljudi*	36 (24%)	150	p>0.05	8 (18.2%)	44	p>0.05	p>0.05
Allergies *Alergije*	39 (26%)	150	p<0.05	17 (38.6%)	44	p>0.05	χ^2=0.104 p>0.05
Smokers *Pušači*	39 (26%)	150	p<0.05	4 (9.1%)	44	p<0.05	χ^2=0.018 P<0.05
Flu-cold more than once a year/*Grip-prehlada više od jedanput godišnje*	96 (64%)	150	p<0.05	25 (56.8%)	44	p>0.05	χ^2=0.387 p>0.05
Fungiform papillae <100 *Broj pečurkastih papila <100*	44 (52.4%)	84	p>0.05	12 (41.4%)	29	p>0.05	χ^2=0.307 p>0.05
Fungiform papillae >100 *Broj pečurkastih papila >100*	40 (47.46%)	84	p>0.05	17 (58.6%)	29	p>0.05	

Table 2. Analysis of outcome significance within and between the two groups
Tabela 2. *Analiza značaja ishoda unutar grupa i između dve grupe*

	Group 1: with sense loss *Grupa 1: sa gubitkom čula*	Total *Ukupno*	χ^2 test in Group *1/χ^2 test u okviru grupe 1*	Group 2: without sense loss *Grupa 2: bez gubitka čula*	Total *Ukupno*	χ^2 test within Group 2/ *χ^2 test u okviru grupe 2*	χ^2 test between the two groups *χ^2 test između dve grupe*
Clinical presentation-predominantly respiratory *Klinička prezentacija – dominantno respiratorna*	35 (23.3%)	150	p>0.05	12 (27.3%)	44	p>0.05	
Clinical presentation-predominantly neurological *Klinička prezentacija – dominantno neurološka*	69 (46%)	150	p<0.05	23 (52.3%)	44	p<0.05	χ^2=0.417 p>0.05
Clinical presentation-other symptoms/*Klinička prezentacija – ostalo*	46 (30.7%)	150	p>0.05	9 (20.4%)	44	p>0.05	
Clinical presentation-mild *Klinička slika – blaga*	36 (24%)	150	p>0.05	5 (11.4%)	44	p>0.05	
Clinical presentation-moderate *Klinička slika – umerena*	105 (70%)	150	p<0.05	37 (84.1%)	44	p<0.05	χ^2=0.164 p>0.05
Clinical presentation-severe *Klinička slika – teška*	9 (6%)	150	p>0.05	2 (4.5%)	44	p>0.05	
Hospitalized *Hospitalizovani*	4 (2.7%)	150	p>0.05	3 (6.8%)	44	p>0.05	χ^2=0.194 p>0.05
Non-hospitalized *Nehospitalizovani*	146 (97.3%)	150	p<0.05	41 (93.1%)	44	p<0.05	
Post-COVID-predominantly respiratory/*Postkovid – dominantno respiratorni*	44 (29.3%)	150	p<0.05	10 (22.7%)	44	p>0.05	
Post-COVID- predominantly neurological/*Postkovid – dominantno neurološki*	36 (24%)	150	p<0.05	13 (29.6%)	44	p>0.05	χ^2=0.001 p<0.05
Post-COVID-other *Postkovid – ostalo*	47 (31.3%)	150	p>0.05	0 (0%)	44	p>0.05	
Without Post-COVID syndrome/*Bez Postkovid sindroma*	23 (15.3%)	150	p>0.05	21 (47.7%)	44	p>0.05	

and a lack of hospitalization was noted. No statistical significance was observed regarding the type of Post-COVID symptoms. The most notable disparity between the two groups pertained to the presence of Post-COVID symptoms, including cardiovascular, gastrointestinal symptoms, skin changes, and reactivation of herpes simplex virus (p<0.05), which were significantly more frequently in Group 1 **(Table 2).**

When comparing the number of fungiform papillae with the onset day of taste loss symptoms, it was observed that a slightly higher proportion of subjects with fewer papillae experienced taste loss within the first to third day, whereas a slightly larger proportion of subjects with a greater number of papillae lost their sense of taste between the fourth and sixth day. However, these differences did not reach statistical significance **(Table 3).**

Additionally, when comparing the number of fungiform papillae in the anterior third of the tongue with the duration of taste loss symptoms, no statistically significant differences were found **(Table 4).**

Furthermore, comparing the number of fungiform papillae in the anterior third of the tongue with the intensity of taste loss symptoms revealed no statistically significant differences **(Table 5).**

Upon analyzing the intensity of the loss of the sense of smell and/or taste, it was revealed that 82% of respondents reported a complete loss of the sense of smell (anosmia), while 18% experiences a partial loss (hyposmia). Additionally, 54% indicated a complete loss of the sense of taste (ageusia), whereas 46% reported a partial loss (hypogeusia). Concerning the onset of symptoms, 46% of respondents reported experiencing sense loss within the first to third day period, while 45.3% marked the fourth to sixth day, and

Table 3. Comparison of the number of fungiform papillae with the day of taste loss onset
Tabela 3. *Poređenje broja fungiformnih papila sa danom početka simptoma gubitka čula ukusa*

Total 84 *Ukupno 84*	Number of fungiform papillae in the anterior third of the tongue < 100 *Broj pečurkastih papila u prednjoj trećini jezika < 100*	Number of fungiform papillae in the anterior third of the tongue > 100 *Broj pečurkastih papila u prednjoj trećini jezika > 100*	χ^2 test χ^2 *test*
Onset of symptoms of loss of taste in 1-3 days/*Početak simptoma gubitka čula ukusa u okviru 1–3 dana*	25 (29.8%)	16 (19%)	χ^2=0.286 p>0.05
Onset of symptoms of loss of taste in 4-6 days/*Početak simptoma gubitka čula ukusa u okviru 4–6 dana*	15 (17.9%)	20 (23.8%)	
Onset of symptoms of loss of taste in 7-10 days/*Početak simptoma gubitka čula ukusa u okviru 7–10 dana*	4 (4.8%)	4 (4.8%)	

Table 4. Comparison of the number of fungiform papillae with the duration of taste loss
Tabela 4. *Poređenje broja fungiformnih papila sa trajanjem simptoma gubitka čula ukusa*

Total 84 *Ukupno 84*	Number of fungiform papillae in the anterior third of the tongue < 100 *Broj pečurkastih papila u prednjoj trećini jezika < 100*	Number of fungiform papillae in the anterior third of the tongue > 100 *Broj pečurkastih papila u prednjoj trećini jezika > 100*	χ^2 test χ^2 *test*
Duration of taste loss 1-5 days *Trajanje gubitka čula ukusa 1–5 dana*	7 (8.3%)	12 (14.3%)	
Duration of taste loss 6-15 days *Trajanje gubitka čula ukusa 6–15 dana*	20 (23.8%)	20 (23.8%)	χ^2=0.112 p>0.05
Duration of taste loss more than 15 days *Trajanje gubitka čula ukusa više od 15 dana*	17 (20.2%)	8 (9.5%)	

Table 5. Comparison of the number of fungiform papillae with the intensity of taste loss
Tabela 5. *Poređenje broja fungiformnih papila sa intenzitetom simptoma gubitka čula ukusa*

Total 84 *Ukupno 84*	Number of fungiform papillae in the anterior third of the tongue < 100 *Broj pečurkastih papila u prednjoj trećini jezika < 100*	Number of fungiform papillae in the anterior third of the tongue > 100 *Broj pečurkastih papila u prednjoj trećini jezika > 100*	χ^2 *test* χ^2 *test*
Partial taste loss *Delimičan gubitak čula ukusa*	17 (20.2%)	19 (22.6%)	χ^2=0.412 p>0.05
Total taste loss/*Totalni gubitak čula ukusa*	27 (32.1%)	21 (25%)	

8.7% indicated the seventh to tenth day. Regarding the duration of symptoms, 25.3% reported duration of 1-5 days, 45.3% experienced symptoms for 6-15 days, and 29.4% endured symptoms for more than 15 days. Among the various taste sensations, respondents most commonly reported the absence of pleasant taste perception (62%), followed by the inability to perceive salty (20%), sweet (8.7%), sour (6.7%), and bitter (2.7%) tastes. When questioned about experiencing unpleasant tastes without food or drink consumption, 18% of respondents answered affirmatively, though this was not statistically significant. Similarly, when asked about experiencing unpleasant tastes while consuming food or drink that should normally be enjoyable, 28.7% responded positively, also without statistical significance (p>0.05).

Discussion

The focus of this study was to comprehensively examine the clinical manifestation of COVID-19, particularly highlighting symptoms associated with loss of smell and/or taste. Emphasis was placed on identifying predictors based on the constitutional characteristics of the subjects. Our research revealed a higher prevalence of sensory loss symptoms among female subjects, consistent with findings from Lee et al., which noted a greater occurrence of anosmia and ageusia in younger females [9]. The observed higher susceptibility to COVID-19 in humans can be attributed to the increased ease of transmission through interpersonal contact. Interestingly, a substantial proportion of subjects in the anosmia and

ageusia group were found to be non-allergic, corroborating the findings of Licari et al., who suggested that the presence of allergies might act as a protective factor against anosmia [10]. This assertion is supported by the inverse relationship between allergic sensitization and ACE2 receptor expression, where natural allergen exposure significantly reduces ACE2 expression. Additionally, studies by Namiq Faiq et al. [11] and Iqbal et al. [12] highlighted the prevalence of smoking among respondents with loss of smell and/or taste in COVID-19 cases. Although our results confirmed a significant number of smokers among subjects with anosmia and ageusia, stratification by gender revealed a statistically significant difference in the number of non-smoking females experiencing these symptoms, aligning with the results of Talavera et al. [13]. While an association between recurrent influenza/cold episodes and anosmia in COVID-19 patients was anticipated, no statistically significant difference was found between these patients and those without symptoms. Similarly, no statistical significance was found when comparing the number of fungiform papillae with the presence or absence of taste loss symptoms and their intensity, onset, and duration. Tsuchiya et al. [14] and Sakaguchi et al. [15] explained the presence of ACE2 receptors in the papillae themselves, potentially elucidating the results, as the virus binds to these receptors, causing damage irrespective of their quantity. Regarding COVID-19 outcomes, attention was given to clinical imaging, hospitalization, and Post-COVID symptoms. Symptoms occurring in COVID-19 were categorized into three groups: primarily respiratory, predominantly neurological, and others, encompassing cardiovascular, gastrointestinal, and dermatological manifestations. Our findings indicated a significant number of subjects in both experimental and control groups exhibiting predominantly neurological symptoms during COVID-19, supported by Chen et al.'s confirmation of numerous neurological symptoms in COVID-19 patients [16]. Chen et al. confirmed that these neurological symptoms are not specific to this disease, highlighting multiple pathways of neurological damage, including direct neuropathogenic effects of the virus and indirect mechanisms such as hypoxia, dehydration, acute respiratory distress syndrome, and altered pH in the systemic state. Despite Zazhytska et al.'s assertion that anosmia and ageusia are neurological symptoms, our study did not find a significant difference between groups of subjects with and without loss of smell and/or taste [17]. In both groups, various other neurological symptoms were observed. Consistent with Talavera et al.'s findings, anosmia and ageusia were predictors of a favorable disease outcome, with affected patients exhibiting better immune responses [13]. However, our results suggest that the appearance of sensory loss symptoms may not necessarily indicate a milder clinical course, warranting further investigation to address potential sample size disparities. Post-COVID symptoms represent an extension of the disease, emerging after the acute phase. We proposed a classification of acute (lasting up to 4 weeks), continuous (lasting from 4 to 12 weeks), and post-COVID (symptoms developed during or after infection and lasting longer than 12 weeks) phases, in line with Sivan and Taylor's definition of post-COVID symptoms [18]. Our study supported the presence of post-COVID symptoms in both treatment groups, with respiratory and neurological symptoms predominating, as confirmed by Wijeratne et al. [19, 20].

The limitations of the study include the need more detailed results, which could be obtained by increasing the number of participants in both samples and by comparing the results with those related to newer strains of the coronavirus. Additionally, in the future, employing a different method for counting fungiform papillae could potentially enhance the accuracy of the results.

Conclusion

Based on the conducted research, the following conclusions can be drawn:

1. Potential predictors for symptoms of loss of smell and/or taste during COVID-19 include working in professions involving interpersonal contact, non-smoking habits, absence of allergies, and experiencing mild respiratory infections more than once a year.

2. The severity of the clinical course of COVID-19 does not differ significantly between subjects with sensory loss symptoms and those without. However, there is a notable distinction in the types of post-COVID symptoms. Gastrointestinal issues, cardiovascular complications, skin changes, and reactivation of the herpes simplex virus were significantly more prevalent in the group experiencing loss of smell and/or taste.

3. There is no confirmed correlation between the number of fungiform papillae on the anterior third of the dorsal surface of the tongue and the onset time, duration, and intensity of taste loss symptoms, nor with the occurrence of various types of taste disturbances.

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CLADRIBINE IN THE TREATMENT OF HAIRY CELL LEUKEMIA – A SINGLE-CENTRE TEN-YEAR EXPERIENCE

PRIMENA KLADRIBINA U LEČENJU TRIHOLEUKEMIJE − DESETOGODIŠNJE ISKUSTVO JEDNOG CENTRA

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Summary

Introduction. Hairy cell leukemia is a rare, indolent chronic lymphoproliferative disorder characterized by circulating B cells with cytoplasmic projections, pancytopenia, and recurrent infections. This study aims to evaluate the efficacy and safety of cladribine in managing the disease among patients treated at the Clinical Centre of Vojvodina. **Material and Methods**. This study included 34 patients with immunohistochemically confirmed hairy cell leukemia, treated with cladribine from September 2013 to December 2023. Clinical data were reviewed and analyzed using standard statistical methods. **Results.** At the time of cladribine administration, the median age was 53; 50% of patients were symptomatic, 65% had pancytopenia, and 62% presented with splenomegaly. After the first cycle, 68.75% of patients achieved a complete hematologic response, and the overall response rate was 100%. The median follow-up period was 51 months. During this period, two patients were diagnosed with non-melanoma skin cancers, one with renal cell carcinoma, and one with both myelodysplastic syndrome and prostate cancer. Additionally, 88% of patients experienced at least one infection, with viral infections being the most frequent complications. Four patients died during the follow-up period, and the 5-year survival rate was 97%. **Conclusion.** Cladribine is an effective treatment for hairy cell leukemia, demonstrating a good safety profile and potential for long-term remission.

Key words: Cladribine; Leukemia, Hairy Cell; Antineoplastic Agents; Treatment Outcome

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Sažetak

Uvod. Leukemija vlasastih ćelija je retka indolentna hronična limfoproliferativna bolest, koja se karakteriše cirkulišućim B-ćelijama sa citoplazmatskim produžecima, pancitopenijom i učestalim infekcijama. Cilj ovog istraživanja je da se ispita efikasnost i bezbednost kladribina u tretmanu ove bolesti među bolesnicima koji su lečeni u Kliničkom centru Vojvodine. **Materijal i metode.** U studiju su uključena trideset i četiri bolesnika sa imunohistohemijski potvrđenom dijagnozom leukemije vlasastih ćelija koji su lečeni kladribinom od septembra 2013. do decembra 2024. godine. Podaci su obrađeni standardnim statističkim metodama. **Rezultati.** U vreme primene kladribina medijana starosti je bila 53 godine; 50% bolesnika je imalo simptome bolesti, 65% pancitopeniju, a splenomegalija je bila prisutna kod 62% obolelih. Nakon prvog ciklusa lečenja, 68,75% bolesnika je postiglo kompletan hematološki odgovor, a stopa ukupnog odgovora na terapiju je bila 100%. Medijana praćenja je bila 51 mesec. Tokom praćenja, kod dva bolesnika je dijagnostikovan nemelanomski karcinom kože, kod jednog karcinom bubrega, a kod jednog bolesnika mijelodisplastični sindrom i karcinom prostate. Osamdeset i osam posto bolesnika je imalo najmanje jednu infekciju, najčešće virusnu. Četiri bolesnika su preminula tokom perioda praćenja. Petogodišnje preživljavanje iznosi 97%. **Zaključak.** Kladribin pokazuje visoku efikasnost u lečenju bolesnika sa triholeukemijom i dovodi do dugotrajnih remisija, uz relativno povoljan bezbedonosni profil.

Ključne reči: kladribin; leukemija vlasastih ćelija; antineoplastični agensi; ishod lečenja

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Introduction

Hairy cell leukemia (HCL), also known as tricholeukemia, is a rare, indolent chronic lymphoproliferative disorder that accounts for 2-3% of all leukemias [1, 2]. Initially described as leukemic reticuloendotheliosis [3, 4], it was later established that the cell of origin is a mature B cell [5]. In 2008, the WHO classification of lymphoid neoplasms distinguished a variant form from the classical form of HCL (cHCL) [6]. cHCL is four to five times more frequent in men than in women [2, 7], and the median age at diagnosis of HCL is approximately 55 years [5, 8].

HCL is characterized by circulating B cells with cytoplasmic projections, pancytopenia, and recur-

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Abbreviations

HCL – Hairy Cell Leukemia
cHCL – classic Hairy Cell Leukemia
HCLv – Hairy Cell Leukemia variant
CD – Cluster of Differentiation
IFN-α – alpha interferon
CR – complete response
PR – partial remission
TTNT – time to next treatment
RFS – relapse free survival
χ^2 – Chi-square
ORR – overall response rate
HBV – Hepatitis B virus
HZV – Herpes zoster virus
SSTI – skin and soft tissue infections
HSV – Herpes simplex virus

rent infections. Early studies reported splenomegaly in more than 90% of patients, but this has become a less prominent feature, presumably due to earlier detection through routine blood examination [9, 10]. A relatively characteristic manifestation of tricholeukemia is monocytopenia in the peripheral blood, though monocytes may be erroneously reported by automated hematology analyzers [10, 11].

The immunophenotypic profile of the leukemic cells is crucial for establishing the diagnosis. The characteristic immunophenotype of CD11c+, CD25+, CD103+, CD123+, along with pan B cell surface antigens (CD19+, CD20+, CD22+), confirms the diagnosis of cHCL [9, 11]. Unlike the HCL variant (HCLv), these cells are intensely stained for CD200 expression and negatively stained for CD27 antigen [11]. A trephine bone marrow biopsy and aspirate are important for assessing the extent of bone marrow infiltration [11].

Historically, splenectomy was the treatment of choice, leading to the elimination of abdominal disturbances and the amelioration of peripheral blood cytopenias [12, 13]. However, with limited therapeutic options, the results were modest, with a median survival time of 4 to 6 years [14]. Since the mid-1980s, therapies have significantly improved with the introduction of three new drugs: alpha interferon (IFN-α) in 1984, and the purine nucleoside analogues pentostatin in 1986 and cladribine in 1990 [15]. However, the use of IFN-α often led to disappointingly low complete response rate, with only partial and short-lived responses [16]. Cladribine (2-chlorodeoxyadenosine) has become universally accepted as the agent of choice in treating HCL, with high CR rates, long-term remissions, minimal toxicity and normal life expectancy [8, 17, 18].

In the relapsed or refractory setting, novel therapeutic options, like rituximab, rapidly accelerated fibrosarcoma B-type/mitogen-activated extracellular signal-regulated kinase (BRAF/MEK) inhibitors, and Bruton Tyrosine Kinase inhibitors, have shown promising results [19].

The aim of this study was to evaluate the efficacy and safety of cladribine in the treatment of cHCL among patients treated at the University Clinical Centre of Vojvodina, with attention particular focus on response rates, survival, infectious complications, and secondary malignancies.

Material and Methods

From September 2013 through December 2023, 34 patients were treated with cladribine at the Hematology Clinic, University Clinical Centre of Vojvodina. The patients were previously diagnosed with cHCL based on the World Health Organization criteria through morphological and immunohistochemical analysis of the bone marrow.

Treatment was initiated in cases of symptomatic organomegaly, declining hematologic parameters (hemoglobin <10 g/dL, platelet count <100,000/mL or absolute neutrophil count <1,000/mL) and/or the presence of systemic symptoms.

A single course of cladribine was administered as a subcutaneous bolus injection at a daily dose of 0.14 mg/kg body weight for five consecutive days. Bone marrow evaluation after treatment was primarily conducted in cases with unclear cytopenia. Responses were determined using standard response criteria regarding complete blood count and splenomegaly, four to six months post-treatment. Complete remission (CR) was defined as near normalization of peripheral blood counts and resolution of organomegaly. Partial remission (PR) was described as more than 50% improvement in cytopenia and organomegaly. Reappearance of hairy cells in peripheral blood or bone marrow was considered a relapse after CR, while progression after PR was defined as greater than 50% increase in residual disease [20].

The clinical database was reviewed retrospectively. Demographic features, as well as clinical and laboratory findings, were collected from medical records. Data regarding secondary malignancies, infectious complications, and survival were supplemented by telephone interviews with the patients or their physicians.

The study was approved by the University Clinical Center Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Data were analyzed using descriptive statistics. Categorical variables were summarized as frequencies and percentages, while continuous variables were summarized as median values and range. Since HCL is an indolent disease that does not necessarily require immediate treatment in case of relapse, time to next treatment (TTNT) was considered a more relevant parameter than relapse-free survival (RFS). TTNT was measured from the date of treatment initiation to the date of retreatment for patients achieving a CR or PR. Observations of TTNT were censored at the date of the last contact for patients with no report of relapse or retreatment who were last known to be alive. Overall survival

Table 1. Patient characteristics (n=34)
Tabela 1. *Karakteristike obolelih (n=34)*

Median age at diagnosis, years (range)/*Medijana starosti pri dijagnozi, godine (opseg)*	52 (30–83)
Median age at the time of treatment with cladribine, years (range) *Medijana starosti u vreme lečenja kladribinom, godine (opseg)*	53 (38–83)
Male : female (n/n) (ratio)/*Muškarci : žene (n : n) (odnos)*	(26:8) (3.25:1)
Symptomatic disease, n (%)/*Simptomatska bolest, n (%)*	17 (50%)
Pancytopenia, n (%)/*Pancitopenija, n (%)*	22 (64.7%)
Splenomegaly, n (%)/*Splenomegalija, n (%)*	21 (61.76%)
Hemoglobin at baseline, median (range) (g/L) *Hemoglobin pred započinjanje lečenja, medijana (opseg) (g/L)*	110 (71–156)
Platelet count at baseline, median (range) ($x10^9$/L) *Broj trombocita pred započinjanje lečenja, medijana (opseg) ($x10^9$/L)*	64 (17–269)
White blood cell count at baseline, median (range) ($x10^9$/L) *Broj leukocita pred započinjanje lečenja, medijana (opseg) ($x10^9$/L)*	2.69 (0.65–20.2)
Follow-up (months), median (range)/*Praćenje (meseci), medijana (opseg)*	51 (0.3–148)

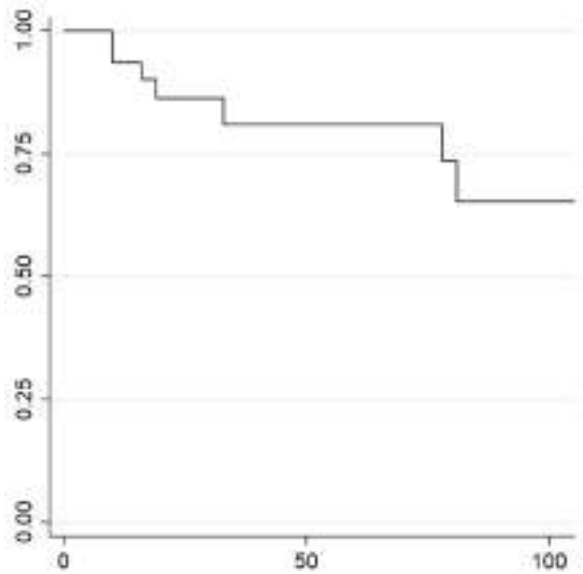
was measured from the date of diagnosis to the event of death. Patients last known to be alive were censored. Overall survival was estimated using Kaplan-Meier analysis. Statistical analyses were performed using Stata statistical software. Chi-square test (χ^2) was used to determine if there was a statistically significant difference in complete response rates between patients treated with cladribine frontline and second-line, with a p-value of <0.05 was considered to be statistically significant.

Results

We report on 34 cHCL patients treated with cladribine, of whom 32 were evaluable for response. The median age at diagnosis was 52 years (range 30–83). Clinically, 62% of patients presented with splenomegaly, 65% had pancytopenia and 50% were symptomatic. Patient characteristics are presented in **Table 1.** Bone marrow biopsy histological findings at diagnosis were available in 27 (79%) cases and showed a 64% medullary infiltration by hairy cells, on average.

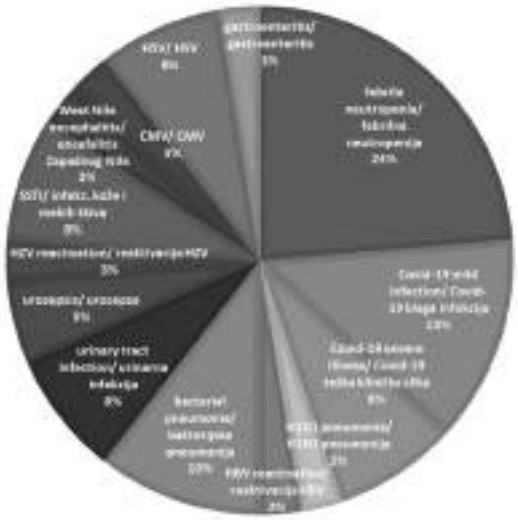
The median age at the time of cladribine administration was 53 years (range 38 to 83). Cladribine was administered as a first-line treatment to 20 (59%) patients and as a second-line treatment in 14 (41%) patients (after IFN-α). It appeared to be equally effective as both first- or second-line therapy (χ^2=0.22, p=0.63). Among the 32 patients evaluable for response, 22 (68.75%) achieved CR after one cycle of cladribine. The overall response rate (ORR) was 100%.

Eight relapsing patients received another course of cladribine, 10–118 months after the first cycle (median 26 months), and one of them received a third cycle as well. One patient was treated with rituximab and vemurafenib 26 months after the second course of cladribine, while rituximab alone was administered in another case, eight years after the cladribine retreatment. Follow-up period ranged from 0.3 to 148 months (median follow-up 51 months). The Kaplan-Meier progression-free survival (PFS) estimation curve is shown in **Graph 1.**

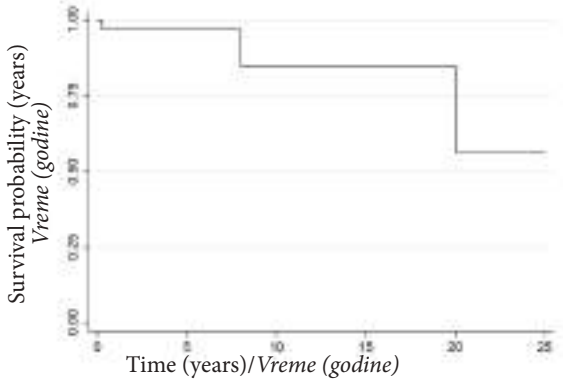


Graph 1. RFS probability
Grafikon 1. *Verovatnoća preživljavanja bez relapsa*

During the follow-up period, two patients were diagnosed with non-melanoma skin cancers, one patient with renal cell carcinoma, and one with myelodysplastic syndrome and prostate cancer. Eighty-eight percent of patients experienced at least one infection during follow-up, with viral infections being the most frequent complications **(Graph 2).** Four out of 34 patients died during the follow-up period – two of them due to viral pneumonia (H1N1 and Covid-19), one due to uncontrolled hairy cell leukemia, and one due to Gram-negative bacterial sepsis, occurring a week after therapy administration. The 5-year overall survival rate was 97% **(Graph 3)**.



Graph 2. Infections detected during the follow-up period. *HBV – Hepatitis B virus; HZV – Herpes zoster virus infection; SSTI – skin and soft tissue infections; CMV – Cytomegalovirus infection; HSV – Herpes simplex virus*
Grafikon 2. *Infekcije zabeležene tokom perioda praćenja. HBV – Hepatitis B virus; HZV – Herpes zoster virusna infekcija; SSTI – infekcija kože i mekih tkiva; CMV – citomegalovirusna infekcija; HSV – Herpes simplex virus*



Graph 3. Overall survival
Grafikon 3. *Ukupno preživljavanje*

Discussion

In this study, as expected based on previous observations [2, 7, 21], there is a higher proportion of men than women among the patients with cHCL. However, the ratio is slightly skewed towards women, which might be a consequence of the relatively small cohort size, constituting the biggest limitation of the analysis. Most of the patients were between 50 and 70 years old at the time of diagnosis and treatment, aligning with commonly reported data in the literature [2, 15, 17].

Symptomatic disease (B symptoms and/or symptomatic organomegaly) was present in half of our patients before cladribine initiation. The available literature does not specify whether patients had symptoms before the therapy. However, a recent study from Czech Republic reported that indication for first-line treatment was the presence of B symptoms and symptomatic organomegaly in 13.7% and 42.9% of patients, respectively [22]. While these results are similar to ours, they are not entirely comparable due to differences in reporting. Regarding splenomegaly, several studies report similar results, with 67% (among 45 subjects) and 66.5% (among 221 subjects) of patients having splenomegaly at baseline [17, 23]. An Italian study published two years ago, which included patients treated between March 1991 and May 2019 across 18 hematology centers, reported a slightly lower prevalence of splenomegaly (46.9% of 513 patients) [21]. An even lower prevalence (33.3% of 123 patients) was observed among patients treated in the French region of Western Normandy between 1996 and 2016 [2]. These differences could be attributed to variations in study group sizes and the timing of diagnosis. In the French study, 20.3% of patients had pancytopenia [2], but other literature often does not specify the number of patients with pancytopenia, or specifies only mean values and range of individual parameters, making direct comparisons challenging [8, 9, 17, 21, 23, 25].

In our cohort, the ORR to cladribine was 100%, with 68.75% achieving CR and 31.25% achieving PR. Similar data can be found in other studies, with ORR up to 100% and a variable proportion of CR ranging from 48.6 to 95% [17, 21, 23–25]. According to current recommendations, response assessment includes evaluating hematologic parameters, physical examination with spleen size estimation, and bone marrow biopsy, typically delayed for 4 to 6 months after drug administration is completed [11]. The literature observes that the CR percentages increase over time, from 80% after 3-4 months to nearly 100% after 6 months [17, 26]. Therefore, inconsistent results among studies can partially be explained by differences in the timing and method of response assessment, which are usually not clearly stated. The retrospective nature of our study is a significant drawback.

In our study, TTNT ranged from 10 to 118 months (median 26 months) after the first cycle of cladribine. Similar results were published in 2003, where 209 patients werw treated with cladribine and had at least 7 years of follow-up from April 1986 to November 2000. In these patients, time to relapse after the first course of cladribine ranged from 8 to 118 months [25]. Other studies reported different results, with a median TTNT ranging from 28 to 147 months [2, 27]. Notably, the median TTNT of 28 months was observed in a study targeting patients aged 70 and over, where the CR percentage was lower than in most studies (71%). Older age at diagnosis has been associated with worse prognosis in other studies as well [28].

Non-melanoma skin cancers are the most common secondary malignancies in our group, consistent with other studies that followed HCL patients for several decades after cladribine administration. Secondary malignancies developed in about 20% of these patients [23, 25]. The proportion is lower in our cohort – four out of 34 (11.7%), but the sam-

ple size is also much smaller compared to studies that included around 200 patients each [23, 25].

Purine nucleoside analogs are known to cause serious myelosuppression, and a high risk of severe infections, particularly in the initial treatment phase. The incidence of infections ranges from 30 to 50% [21, 29], with respiratory tract infections being the most common [21, 30]. The higher rate of infections in our study may partly be explained by the follow-up period, which included the COVID-19 pandemic.

The 5-year and 10-year overall survival predicted here does not significantly differ from those reported in other studies [21, 23, 31].

With modern therapeutic options, HCL has transitioned from a deadly illness to a disease with a favorable prognosis, where life expectancy among patients is similar to the general population [23, 31, 32]. However, increased susceptibility to infections, both in the initial phase and during post-therapeutic bone marrow suppression, necessitates great caution, particularly regarding preventive measures and timely initiation of treatment with purine analogs before blood parameters decline to dangerous levels or before a patient acquires an active infection. The updated Hairy Cell Leukemia Foundation guidelines consider off-label treatment options with vemurafenib for patients with HCL who have pancytopenia and an active uncontrolled infection [33, 34]. The use of myeloid growth factors should be considered individually for each patient with an active infection [11, 21]. Live virus vaccines should be avoided, though patients may receive vaccines containing inactivated viral pathogens, despite limited evidence on the development of an adequate immune response in these patients [11].

Conclusion

Although the number of patients in our cohort is a limiting factor, we can conclude that cladribine demonstrates high efficacy in the treatment of hairy cell leukemia patients, leading to long-term remissions with a relatively favorable safety profile. Nowadays, these patients have near-normal life expectancy, comparable to the general population. However, due to their increased risk of developing secondary malignancies, long-term follow-up is mandatory. The challenge of managing infections remains a unique aspect of treating these patients. For those who are relapsed or refractory to purine nucleoside analogs, several targeted drugs have shown considerable promise in clinical trials.

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ASSESSMENT OF CARDIOVASCULAR RISK IN PATIENTS WITH TYPE 2 DIABETES AND ALBUMINURIC DIABETIC KIDNEY DISEASE PHENOTYPE

ANALIZA KARDIOVASKULARNOG RIZIKA KOD OSOBA SA TIPOM 2 DIJABETESA I ALBUMINURIČNIM FENOTIPOM DIJABETESNE BOLESTI BUBREGA

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Summary

Introduction. The aim of this study is analysis of cardiovascular risk in non-albuminuric and albuminuric patients with type 2 diabetes and diabetic kidney disease. **Material and Methods**. The study included 136 patients with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate <90 ml/min/1.73 m^2). Patients were divided into two groups: Group A (patients without albuminuria) and Group B (patients with albuminuria). The cardiovascular risk was assessed through a retrospective analysis of data from electronic medical records. **Results**. We found statistically significantly more patients with stage 3a (Group A: 10% vs. Group B: 54%) and stage 3b (Group A: 7% vs. Group B: 13%; p<0.05) chronic kidney disease in the albuminuric group. These patients also had a longer duration of diabetes (Group A: 13.43±9.56 vs. Group B: 17.14±9.17 years; p<0.05), a higher frequency of male subjects (Group A: 44% vs. Group B: 63.9%; p<0.05) and a higher prevalence of smokers. The presence of hypertension was significantly more frequent in Group B (Group A: 89% vs. Group B: 97.2%; p<0.05). There was no significant difference between the groups in terms of age and metabolic control. However, coronary heart disease (Group A: 36% vs. Group B: 55.6%; p<0.05), peripheral artery disease (Group A: 16% vs. Group B: 22.2%; p<0.05), and stroke (Group A: 5% vs. Group B: 22.2%; p<0.05) were significantly more common in patients with type 2 diabetes and albuminuria. **Conclusion.** The albuminuric phenotype of diabetic kidney disease is associated with greater kidney function impairment, a longer duration of diabetes, and a higher prevalence in men. The presence of albuminuria significantly increases cardiovascular risk in people with type 2 diabetes and chronic kidney disease. Using renoprotective antihyperglycemic agents is essential in this group of patients, as they have an increased mortality risk.

Key words: Cardiovascular Diseases; Risk Factors; Diabetes Mellitus, Type 2; Diabetic Nephropathies; Renal Insufficiency, Chronic ; Albuminuria; Phenotype

Sažetak

Uvod. Cilj ove studije je analiza kardiovaskularnog rizika kod osoba bez albuminurije i osoba sa albuminurijom i sa tipom 2 dijabetesa i dijabetesnom bolešću bubrega. **Materijal i metode.** Studija je obuhvatila 136 bolesnika sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom (procenjena brzina glomerulske filtracije < 90 ml/min/1,73 m^2). Na osnovu prisustva albuminurije, analiza je sprovedena u dve grupe: grupa A bolesnici bez albuminurije i grupa B bolesnici sa albuminurijom. Analiza kardiovaskularnog rizika je sprovedena retrospektivnom analizom podataka iz istorija bolesti. **Rezultati.** Registrovano je statistički značajno više pacijenata sa stadijumom 3a (A: 10% vs B: 54%) i 3b (A: 7% vs B: 13%; p < 0,05) hronične bubrežne insuficijencije u grupi pacijenata sa albuminurijom. U ovoj grupi registrovano je značajno duže trajanje dijabetesa (A: 13,43 ± 9,56 vs B: 17,14 ± 9,17 godina; p < 0,05), značajno veća učestalost muškog pola (A: 44,0% vs B: 63,9%; p < 0,05) i navike pušenja. Takođe registrovano je značajno češće prisustvo arterijske hipertenzije (A: 89% vs B: 97,2%; p < 0,05). U analiziranoj kohorti pacijenti se nisu razlikovali u pogledu godina starosti i metaboličke kontrole. Koronarna bolest je bila značajno češće prisutna kod bolesnika sa tipom 2 dijabetesa i albuminurijom (A: 36,0% vs B: 55,6%; p < 0,05) kao i periferna vaskularna bolest (A: 16% vs B: 22,2%; p < 0,05) i cerebrovaskularni insult (A: 5% vs B: 22,2%; p < 0,05). **Zaključak.** Albuminurični fenotip dijabetesne bolesti bubrega je praćen većim stepenom oštećenja bubrežne funkcije, dužim trajanjem dijabetesa i češći je kod muškaraca. Prisustvo albuminurije značajno povećava kardiovaskularni rizik kod osoba sa tipom 2 dijabetesa i hronične bubrežne bolesti u vidu češće pojave koronarne, periferne vaskularne bolesti i cerebrovaskularnog insulta. S obzirom da ove osobe imaju povećanu stopu mortaliteta neophodna je pravovremena terapija primenom renoprotektivnih antihiperglikemijskih lekova.

Ključne reči: kardiovaskularne bolesti; faktori rizika; dijabetes melitus tip 2; dijabetesna nefropatija; hronična bubrežna insuficijencija; albuminurija; fenotip

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Abbreviations

T2D – type 2 diabetes
CVD – cardiovascular disease
CKD – chronic kidney disease
DKD – diabetic kidney disease
eGFR – estimated glomerular filtration rate
BMI – body mass index
HbA1c – glycated hemoglobin
AST – aspartate aminotransferase
ALT – alanine aminotransferase
g-GT – gamma-glutamyl transpeptidase
LDL-C – low-density lipoprotein-cholesterol
HDL-C – high-density lipoprotein-cholesterol
TC – total cholesterol
TG – triglycerides
CRP – C-reactive protein
SD – standard deviation
SGLT2 – sodium-glucose cotransporter 2

Introduction

The number of people with diabetes, a multifactorial disorder affecting the metabolism of carbohydrates, lipids, and proteins, is increasing worldwide. According to the International Diabetes Federation (IDF) data from 2021, an estimated 10.5% of the global population lives with diabetes, and this number is expected to rise to 12.2% by 2045. Diabetes is considered a direct cause of more than 1.5 million deaths per year [1–3].

Type 2 diabetes (T2D) accounts for 90% of the global burden and is considered the "equivalent of cardiovascular risk" [4]. Patients with T2D have a 2 to 4 times higher risk of cardiovascular diseases such as coronary heart disease, cerebrovascular and peripheral vascular disease. Consequently, people with T2D face a significantly increased risk of mortality, especially after the age of 45 [5, 6]. This increased risk is associated with insulin resistance and hyperinsulinemia, endothelial dysfunction, dyslipidemia, hypertension, obesity, hypercoagulability, and low grade inflammation.

Diabetic kidney disease (DKD) is clinically defined as diabetes with persistent albuminuria (albumin-to-creatinine ratio ≥30 mg/g) and/or a persistently low estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m^2) [7]. T2D is the leading cause of chronic kidney disease (CKD) worldwide, and one-third of diabetes patients suffering from (CKD). CKD is a major risk factor for cardiovascular events in people with T2D [3, 7]. The risk of cardiovascular diseases is 6-7 times higher in people with DKD, and the presence of albuminuria significantly increases this risk [7–9]. The first clinical manifestation of DKD is often the presence of albuminuria. However, it is now recognized that, in addition to the classic clinical course, there can also be a reduction in renal function in normoalbuminuric patients. Recent observations indicate that 20-40% of T2D patients have reduced kidney function even in the absence of pathological albuminuria. This group of patients is identified as having the "non-albuminuric" phenotype of DKD. The pathogenesis of this phenotype is unclear, but certain clinical and pathological characteristics are hypothesized. Risk factors for non-albuminuric DKD include female gender, hypertension, active smoking, and the use of renin-angiotensin-aldosterone system inhibitors [10–16].

The aim of this study was to analyze cardiovascular risk in non-albuminuric and albuminuric patients with T2D and CKD during a retrospective study at the Clinic for Endocrinology, Diabetes and Metabolic Diseases of the University Clinical Center of Serbia.

Material and Methods

This retrospective study was conducted at the Clinic for Endocrinology, Diabetes and Metabolic Diseases of the University Clinical Center of Serbia in Belgrade. Initially, the study included 267 patients with type 2 diabetes (T2D) who were hospitalized at the Department for Metabolic Disorders, Intensive Treatment and Cell Therapy in Diabetes from 2018 to 2022. After excluding patients with normal kidney function (eGFR ≥90 ml/min/1.73 m^2), we analyzes 135 patients with CKD. These patients were divided into two groups: patients without albuminuria (group A, N=100) and patients with albuminuria (group B, N=35). Albuminuria was verified as albumin excretion rate of 30-300 mg/24 h in two separate samples, in the absence of urinary tract infection.

We recorded anthropometric data, including body mass index (BMI), calculated as BMI = weight (kg)/height (m^2), and socio-epidemiological data, including age, gender, duration of diabetes, smoking habits, and presence of arterial hypertension. We also noted current therapies for diabetes, hypertension and dyslipidemia.

Biochemical parameters recorded included glycated hemoglobin (HbA1c), hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (g-GT), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), creatinine, uric acid, and C-reactive protein (CRP).

We documented the presence of chronic complications of diabetes, including macrovascular complications (coronary artery disease, stroke, and peripheral vascular disease) and microvascular complications (nephropathy, neuropathy and retinopathy).

The glomerular filtration rate (GFR) was calculated using the MDRD (Modification of Diet in Renal Disease Study) equation, based on gender, age, race and serum creatinine values. CKD stages were defined as follows: stage 1 without kidney failure (eGFR≥90 ml/min/1.73 m^2), stage 2 (eGFR 60-89 ml/min/1.73 m^2), stage 3a (eGFR 40-59 ml/min/1.73 m^2), stage 3b (eGFR 30-44 ml/min/1.73 m^2), stage 4 (eGFR 15-29 ml/min/1.73 m^2) and stage 5 (eGFR<15 ml/min/1.73 m^2).

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software (Advanced Statistics, version 22.0, Chicago, IL, USA). Data are presented as mean±standard deviation (SD), median, and frequencies (%).Normal distribution was tested using the Kolmogorov-Smirnov test. Differences

Table 1. Socio-demographic and anthropometric characteristics of patients with T2D and CKD (mean ± standard deviation or frequency).
Tabela 1. *Socio-demografske i antropometrijske karakteristike osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom (aritmetička sredina ± standardna devijacija ili učestalost)*

Parameter/*Parametar*	Group A/*Grupa A*	Group B/*Grupa B*	Significance/*Značajnost*
Age (years)/*Starosna dob (godine)*	67.03±9.74	68.58±9.46	p=NS
Sex (M/F)/*Pol (M/Ž)*	44/56%	63.9/36.1%	p<0.05
Diabetes duration (years) *Dužina trajanja dijabetesa (godine)*	13.43±9.56	17.14±9.17	p<0.05
BMI (kg/m^2)/*ITM (kg/m^2)*	30.7±2.1	31.4±1.7	p<0.05
Smoking/*Pušenje*	26%	33.3%	p<0.05
Arterial hypertension/*Hipertenzija*	89%	97.2%	p<0.05

Legend: BMI - body mass index; *Legenda: ITM – indeks telesne mase*

were tested for significance using Student's *t*-test, for numeric characteristics and Mann-Whitney U test for nonparametric data. The chi-square test was used for categorical characteristics. A two-sided *p*- value <0.05 was considered statistically significant.

Results

The socio-demographic and anthropometric characteristics of the patients are shown in **Table 1**.

There was a significant difference in the duration of diabetes, with a statistically longer duration recorded in the group with albuminuria (Group A: 13.43±9.56 years vs. Group B: 17.14±9.17 years; p<0.05). Additionally, a statistically significantly higher frequency of male subjects was registered in a group of patients with T2D and albuminuria (Group A: 44% vs. Group B: 63.9%; p<0.05). There was no significant difference in age among the patients (Group A: 67.03±9.74 years vs. Group B: 68.58±9.46 years; p>0.05). Both groups were overweight or obese, with no statistically significant difference in BMI (Group A: 30.7±2.1 vs. Group B: 31.4±1.7, p>0.05).

A statistically significant higher frequency of smokers was found in albuminuric patients with T2D (Group A: 26% vs. Group B: 33.3%; p<0.05).

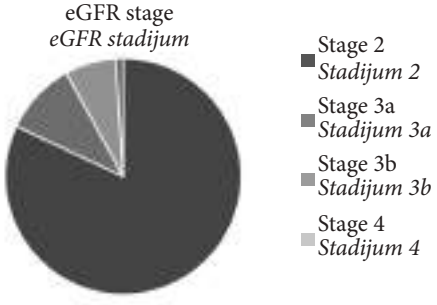
In the group of patients without albuminuria (Group A), the highest percentage of patients had stage 2 CKD (82%), followed by stage 3a (10%), stage 3b (7%), and stage 4 (1%) (p<0.05). In contrast, in the group of patients with albuminuria (Group B), 27.8% had stage 2, 47.2% had stage 3a, 11.1% had stage 3b, and 13.9% of patients had stage 4 CKD (p<0.05). Terminal stage CKD was not recorded in either group.

Analyses revealed a significant difference in average eGFR value between the groups, with a significantly lower eGFR observed in the group of patients with albuminuria (Group A: 53.78±9.24 vs. Group B 69.136±9.37, p<0.05),as shown in **Graphs 1 and 2**.

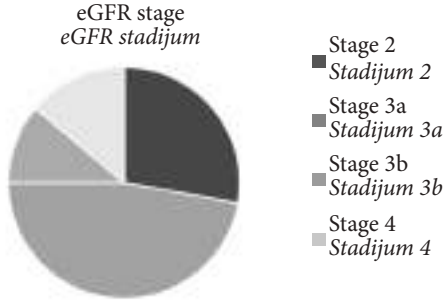
The albuminuric group also had significantly higher creatinine (Group A: 89.66±26.51 vs. Group B: 124.53±49.44 μmol/L; p<0.01) and uric acid levels (Group A: 337.67±81.65 vs. Group B: 372.82±87.66 mmol/l; p<0.05), as shown in **Table 2.**

There were no differences in the parameters of long-term metabolic control, such as HbA1c (Group A: 9.73±2.11 vs. Group B: 9.24±1.85; p>0.05).

Similarly, the lipid profile parameters showed no statistically significant differences between the group (TC: 4.63±1.17 vs. 4.28±1.03; LDL-C: 4.18±1.51 vs. 2.33±0.81; HDL-C: 1.07±0.31 vs. 0.96±0.27; TG:



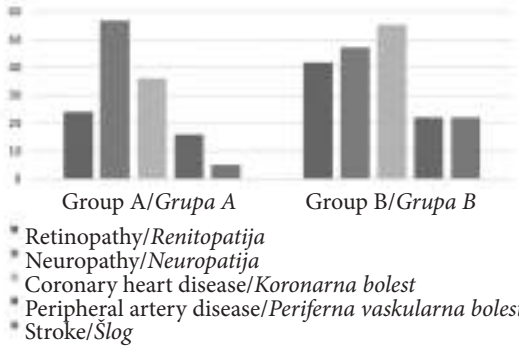
Graph 1. eGFR stages in patients with T2D and CKD without albuminuria
The values are presented as frequencies.
Grafikon 1. *eGFR stadijumi kod osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom bez albuminurije*
Vrednosi su prikazane kao učestalosti.



Graph 2. eGFR stages in patients with T2D and CKD with albuminuria
The values are presented as frequencies.
Grafikon 2. *eGFR stadijumi kod osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom sa albuminurijom*
Vrednosti su prikazane kao učestalosti.

Table 2. Metabolic and biochemical parameters of patients with T2D and CKD (mean ± standard deviation or frequency).
Tabela 2. *Metabolički i biohemijski parametri kod osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom (aritmetička sredina ±standardna devijacija ili učestalost)*

Parameter/*Parametar*	Group A/*Grupa A*	Group B/*Grupa B*	Significant/*Značajnost*
Creatinine values/*Vrednosti kreatinina (μmol/L)*	89.66±26.51	124.53±49.44	p<0.01
Uric acid/*Mokraćna kiselina (mmol/l)*	337.67±81.65	372.82±87.66	p<0.05
Glycated haemoglobin *Glikozilirani hemoglobin (HbA1c)*	9.73±2.11%	9.24±1.85%	p>0.05
Total cholesterol/*Ukupni holesterol (mmol/l)*	4.63±1.17	4.28±1.03	p>0.05
LDL cholesterol/*LDL holesterol (mmol/l)*	4.18±1.51	2.33±0.81	p>0.05
HDL cholesterol/*HDL holesterol (mmol/l)*	1.07±0.31	0.96±0.27	p>0.05
Triglycerides/*Trigliceridi (mmol/l)*	2.23±1.15	2.35±1.34	p>0.05



Graph 3. Micro- and macrovascular complications in patients with T2D and CKD
The values are presented in percentages. p<0.05; Group A – individuals with T2D without albuminuria; Group B – individuals with T2D and albuminuria
Grafikon 3. *Učestalost mikrovaskularnih i makrovaskularnih komplikacija kod osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom*
Vrednosti su prikazane u procentima. p < 0,05; Grupa A – osobe sa tipom 2 dijabetesa bez albuminurije; Grupa B – osobe sa tipom 2 dijabetesa i albuminurijom

2.23±1.15 vs. 2.35±1.34 mmol/l; p>0.05), as shown in **Table 2**.

Hypertension was significantly more frequent in patients with T2D and albuminuria (Group A: 89% vs. Group B: 97.2%; p<0.05), and these patients were more often on antihypertensive therapy (Group A: 89.0% vs. Group B: 97.2%; p<0.05). However, there were no statistically significant differences in systolic (Group A: 131.95±16.69 vs. Group B: 131.39±18.96 mmHg; p>0.05) or diastolic blood pressure (Group A: 78.15±9.58 vs. Group B: 77.36±10.92 mmHg; p>0.05) between the groups.

A significantly higher number of patients with T2D and albuminuria used aspirin (Group A: 53.0% vs. Group B: 60%; p<0.05) and statins (Group A: 48% vs. Group B: 63.9%; p<0.05). However, there was no statistically significant difference in the current diabetes therapies (metformin, sulphonylureas and insulin) between the groups.

Coronary heart disease was significantly more prevalent in patients with T2D and albuminuria (Group A: 36% vs. Group B: 55.6%; p<0.05) as were peripheral artery disease (Group A: 16% vs. Group B: 22.2%; p <0.05) and stroke (Group A: 5% vs. Group B: 22.2%; p<0.05), as shown in **Graph 3**. The presence of atrial fibrillation was similar between the groups (Group A: 9.0% vs. Group B: 8.3%; p>0.05).

Additionally, retinopathy was more frequent in patients with T2D and albuminuria (Group A: 24% vs. Group B: 41.7%; p<0.05), while neuropathy was more common in patients with T2D without albuminuria (Group A: 57% vs. Group B: 47.2%), as illustrated in **Graph 3**.

Discussion

Our study compared patients with T2D and reduced kidney function (eGFR <90 ml/min/1.73 m^2) between those with albuminuric and non-albuminuric phenotypes. We analyzed various parameters including age, gender, diabetes duration, glomerular filtration rate, creatinine and uric acid levels, lipid profile, presence of hypertension, smoking habits, HbA1c levels, use of aspirin and statintherapy, current diabetes therapy, and macrovascular and microvascular complications.

Previous studies have established that T2D is leading major independent risk factor for chronic kidney disease. Persistent hyperglycemia leads to renal inflammation and tubulointerstitial fibrosis, progressively reducing kidney function [17]. This underscores the importance of regular kidney function monitoring and risk factor management in T2D patients.

Our findings indicate that T2D patients with the albuminuric phenotype have a significantly longer duration of diabetes and on lower average eGFR values, with a higher prevalence of advanced CKD stages. Despite the extended diabetes duration (over 15 years in both groups), none had progressed to end-stage of renal disease. This aligns with previous research suggesting that T2D with CKD and albuminuric phenotype is more prevalent in males [17].

Cardiovascular risk increases with the diabetes duration, and CKD exacerbates the risk in T2D patients [18]. Reduced eGFR independently heightens the risk of cardiovascular complications, including

recurrent myocardial infarctions, left ventricular dysfunction and conduction disorders [19–21].

Our study found that participants with the albuminuric phenotype had a longer diabetes duration and higher incidence of coronary artery disease, peripheral artery disease, and stroke.

Low-density lipoprotein cholesterol is a known independent cardiovascular risk factor, with current guidelines targeting levels below 1.8 mmol/L or 50% reduction from baseline [22, 23].

Despite comparable levels of total cholesterol, LDL cholesterol and triglycerides between the two groups, and higher statin usage in the albuminuric group, neither group achieved the target LDL levels.

The lack of difference in HbA1c levels, which were unsatisfactory, may be attributed to poor glycemic control, the primary reason for hospitalization of these patients.

Hypertension is another independent cardiovascular risk factor, particularly in T2D patients with albuminuria. A meta-analysis of 40 clinical studies highlighted that every 10 mmHg reduction in systolic blood pressure significantly reduces the cardiovascular event frequency [24]. Current guidelines of the American Diabetes Association emphasize controlling all cardiovascular risk factors in T2D patients to prevent complications [23]. Effective management includes high-potency stains, lipid profile, antihypertensive treatment and strict blood pressure control aiming for targets below 130/80 mmHg [22, 23].

Microvascular complications, specifically retinopathy, were significantly more prevalent in T2D and CKD patients with the albuminuric phenotype.

These findings highlight the need for stringent cardiovascular risk management in this group to prevent CKD progression and cardiovascular complications. Achieving adequate glycemic control through antihyperglycemic agents with cardio-renal benefits, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, is crucial for these patients, particularly those with the albuminuric phenotype of DKD [22–26].

Conclusion

The prevalence of albuminuric phenotype of diabetic kidney disease increases with the duration of diabetes and is more common among males. The presence of albuminuria significantly elevates the cardiovascular risk in individuals with type 2 diabetes and chronic kidney disease, manifesting as higher incidence coronary artery disease, peripheral artery disease, and stroke. Therefore, it is essential to use renoprotective antihyperglycemic agents in this group of patients to mitigate the increased mortality risk.

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CHARACTERISTICS OF WEST NILE ENCEPHALITIS IN THE AUTONOMOUS PROVINCE OF VOJVODINA IN THE PERIOD 2021 TO 2022

KARAKTERISTIKE ENCEFALITISA UZROKOVANIH VIRUSOM ZAPADNOG NILA NA TERITORIJI AUTONOMNE POKRAJINE VOJVODINE U PERIODU OD 2021. DO 2022. GODINE

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Summary

Introduction. Neuroinvasive the West Nile virus disease develops in less than 1% of infected individuals, with a mortality rate of approximately 9%. This scientific research aimed to analyze the epidemiological, clinical, and laboratory characteristics, the presence of comorbidities, and the treatment outcome of West Nile encephalitis in 2021 and 2022. **Material and Methods.** The retrospective study includes 33 patients treated at the Infectious Diseases Clinic of the University Clinical Center of Vojvodina from January 1, 2021 to December 31, 2022. The diagnosis was confirmed by serological tests and/or real-time reverse transcriptase polymerase chain reaction of cerebrospinal fluid. **Results.** The study demonstrated a statistically significant predominance of males (57.6%) over females (42.4%) (χ^2=4.5; p=0.03).Individuals over the age of 65 accounted for 51.52% of cases, with the remaining 48.48% being within the working-age population. The highest concentration of cases was observed in the Novi Sad (24.2%). Upon admission, elevated body temperature was prevalent 97% of patients (χ^2 = 8.8; p = 0.03), followed by weakness and malaise in 75.8%, and altered consciousness in 66.7%. Meningeal signs were present in only 48% of patients. Infection was confirmed in all patients through serological analysis of cerebrospinal fluid. A fatal outcome was observed in 31.3% of cases. **Conclusion.** The results of the research indicate that serological analysis is the most reliable method for diagnosing the neuroinvasive form of infection.

Key words: West Nile virus; Encephalitis; Serologic Tests; Signs and Symptoms; Diagnosis; Demography; Treatment Outcome; Risk Factors

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Sažetak

Uvod. Neuroinvazivna bolest razvija se kod manje od 1% inficiranih osoba, sa stopom mortaliteta oko 9%. Cilj je bio analizirati epidemiološke, kliničke, laboratorijske karakteristike, prisustvo komorbiditeta i ishod lečenja encefalitisa uzrokovanog virusom Zapadnog Nila tokom prethodne dve epidemije 2021. i 2022. godine. **Materijal i metode.** Istraživanje je koncipirano kao retrospektivna studija i uključuje 33 pacijenta lečena na Klinici za infektivne bolesti Univerzitetskog kliničkog centra Vojvodine u Novom Sadu u periodu od 1. 1. 2021. do 31. 12. 2022. godine. Dijagnoza je potvrđena serološkim testovima i/ili *real time* reverznom transkripcijom lančane reakcije polimeraze uzorka likvora. **Rezultati.** Rezultatima je dokazana statistički značajno veća zastupljenost muškog pola (57,6%) u odnosu na ženski pol (42,4%) (χ^2 = 4,5; p = 0,03). Tokom navedenih epidemija oboleli su predominantno u uzrasnoj grupi preko 65 godina (51,52%), dok je 16 pacijenata (48,48%) bilo u grupi radno sposobnog stanovništva. Najveća incidencija obolelih je sa prebivalištem na teritoriji opštine Novi Sad (24,2%). Od simptoma na prijemu statistički značajno je dominirala povišena telesna temperatura 97% (χ^2 = 8,8; p = 0,03), slede slabost i malaksalost 75,8% i poremećaj stanja svesti 66,7%. Svega 16 pacijenata (48%) je imalo pozitivne meningealne znake u kliničkom nalazu. Infekcija je kod svih ispitivanih bolesnika potvrđena serološkim analizama likvora. Letalni ishod je registrovan kod 31,3% pacijenata. **Zaključak.** Rezultati istraživanja su pokazali da serološki testovi predstavljaju najpouzdaniju metodu za postavljanje dijagnoze kod neuroinvazivnog oblika infekcije.

Ključne reči: virus Zapadnog Nila; encefalitis; serološki testovi; znaci i simptomi; dijagnoza; demografija; ishod lečenja; faktori rizika

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Introduction

Instances of acute encephalitis necessitate prompt intervention to reduce mortality rates and minimize the neurological sequelae [1, 2]. Among infectious etiologies, the West Nile virus (WNV) stands out as a significant cause, inciting epidemics characterized by febrile illness, meningitis, en-

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Abbreviations

WNV – West Nile Virus
CNS – Central nervous system
RNK – Ribonucleic acid
RT-PCR – Reverse transcription-polymerase chain reaction
ELISA – Enzyme-linked immunosorbent assay
UCCV – University Clinical Center of Vojvodina
CT – Computed tomography
CRP – C-reactive protein

cephalitis, and flaccid paralysis [3]. The WNV, an arbovirus of the Flaviviridae family, is globally disseminated via transmission by Culex mosquitoes, primarily Culex pipiens [4]. Birds are the principal reservoir hosts for WNV in natural ecosystems. Certain mosquito species become infected after feeding on birds with high viremia, and these mosquitoes can then transmit the virus to other vertebrates, including horses and the humans [5]. WNV is believed to replicate initially at the site of inoculation, spreading to regional lymph nodes before entering the bloodstream [6]. The virus infiltrates the central nervous system (CNS) after activating toll-like receptors, in which increase blood-brain barrier permeability by elevating tumor necrosis factor levels [7]. WNV primarily targets neurons in the deep nuclei and gray matter of the brain, as well as in the brainstem and spinal cord [8].

Approximately 80% of WNV infections in humans are asymptomatic, while 20% manifest symptoms such as viral fever [9]. Neuroinvasive disease, affecting less than 1% of those infected, is more likely to occur in immunocompromised and elderly individuals, who are at greater risk of long-term sequelae [10]. Other risk factors for neuroinvasive disease include diabetes, hypertension, and cerebrovascular disease [11].

The clinical spectrum of WNV infection ranges from mild fever to severe symptoms lasting several days to weeks, including debilitating fatigue, pain, weakness, and headaches. Gastrointestinal symptoms and a transient macular rash on the trunk and extremities are sometimes observed [12]. Encephalitis from WNV infection can range from mild disorientation to coma, potentially leading to death [9].

Various diagnostic modalities are available for identifying WNV as the causative agent of CNS infection. Diagnosis is typically confirmed through the detection of viral RNA in serum or cerebrospinal fluid using RT-PCR assays [13, 14]. The detection WNV in cerebrospinal fluid or serum during the acute phase of neurological illness is regarded as a confirmatory diagnostic parameter. WNV-specific antibodies can be detected through ELISA, immunofluorescence assays, neutralization tests, or hemagglutination tests. IgM antibodies appear approximately 4-7 days post-exposure and may persist for about a year, while IgG antibodies can be reliably detected from the eighth day following infection [15].

Patients with WNV encephalitis or focal neurological manifestations often experience prolonged neurological deficits lasting for months or years. The overall mortality rate for neuroinvasive WNV disease is approximately 9% [16].

This study aims to assess the incidence, clinical and epidemiological profiles, gender distribution, association with comorbidities, disease progression, outcomes, and diagnostic methodologies used for detecting the virus in patients diagnosed with WNV encephalitis over the past two years.

Material and Methods

The study was designed as a retrospective study. It included 33 patients diagnosed with WNV encephalitis who were hospitalized at the Infectious Diseases Clinic of the University Clinical Center of Vojvodina (UCCV) between May 2021 and September 2022.

The diagnosis of WNV encephalitis was confirmed through cytobiochemical analysis of cerebrospinal fluid, indicative of viral encephalitis. Etiological diagnosis was established in all patients through multiplex polymerase chain reaction detection of the virus or by detecting elevated levels of IgM antibodies in both cerebrospinal fluid and serum samples. All patients included in the study were aged 18 years or older, and both genders were represented.

Demographic data were collected from admission medical records. Clinical findings included neurological assessments, laboratory analyses of blood and cerebrospinal fluid, cerebrospinal fluid cultures, neurological sequelae, and treatment outcomes.

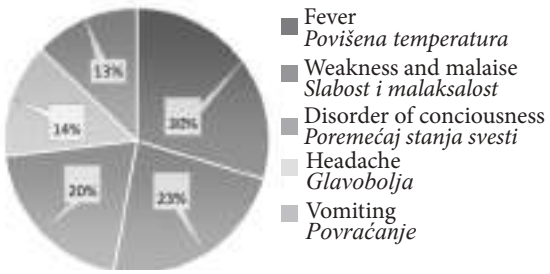
The statistical significance of differences between categorical variables was assessed using the χ^2 test. Continuous variables are presented as the arithmetic mean and standard deviation for normally distributed data, or as the median and interquartile range for data that deviated significantly from normality. The data were retrospectively extracted from medical records. Ethical approval for the study was obtained from the Ethics Committee of the UCCV and the Ethics Board of the Faculty of Medicine in Novi Sad.

Results

The study included 33 patients diagnosed with WNV encephalitis, hospitalized at the Infectious Diseases Clinic of the UCCV from May 2021 to September 2022.

Analyzing gender representation among the examined patients, the total distribution was as follows: 19 out of 33 (57.6%) were male, and 14 out of 33 (42.4%) were female. No statistically significant difference was observed in the distribution of patients by gender (χ^2 test; χ^2=1.551; p=0.213).

The distribution of patients by age indicated a slight predominance of individuals within the geriatric population (>65 years old), comprising 17 out of 33 patients (51.52%). The group of non-geriatric patients (aged 31 to 65 years) included 16 out of 33 patients (48.48%), with no patients in the under-30 age group. The mean age of the patients was 63±34 years (range 38-83 years). Among them, 18 out of 33 patients



Graph 1. Distribution of main symptoms upon admission
Grafikon 1. *Distribucija glavnih simptoma pri prijemu*

(54.5%) predominantly living in rural areas, while 15 out of 33 (45.5%) resided in urban settings, often near a river or forest. The average length of hospital stay was 19±9.4 days, with a range from 1 to 44 days.

All patients had symptoms persisting for more than 24 hours before hospital admission (33 out of 33 cases, 100%). During the two-year study period, 32 out of 33 patients (97%) presented with an elevated temperature as a primary initial symptom prompting medical consultation. Weakness and malaise were the second most common symptoms, affecting 25 out of 33 patients (75.8%) (χ^2=0.330; p=0.566). Disturbances in consciousness ranked third, impacting 22 out of 33 patients (66.7%). Additional symptoms included headaches in 15 out of 33 patients (45.5%), nausea in 14 out of 33 patients (42.2%), and vomiting in 15 out of 33 patients (45.5%). The distribution of symptoms is shown in **Graph 1.** Out of the total number of patients, sixteen exhibited positive meningeal signs upon admission to UCCV, while thirteen out of thirty-three patients displayed neurological signs.

All 33 patients underwent a cranial computed tomography scan upon admission, which revealed no contraindications for performing a lumbar puncture. Cerebrospinal fluid findings consistent with viral encephalitis were observed in all patients. RT-PCR testing was conducted on 31 out of 33 (93.93%) patients, with nine testing positive, accounting for 27.27% of the tests performed. ELISA tests were conducted on all patients using cerebrospinal fluid and serum samples. Positive IgM antibodies were detected in 27 out of 33 patients (81.8%) in both cerebrospinal fluid and blood samples. IgG antibodies were found in the blood samples of 8 out of 33 patients (24.24%) and in the cerebrospinal fluid of 7 out of 33 patients (21.21%). Indicators of the inflammatory response, such as C-reactive protein (CRP) levels, total leukocyte count, and lymphocyte count, were assessed. Elevated CRP levels (CRP>5) were observed in 21 out of 33 patients (63.63%) upon admission, and leukocytosis (leukocyte count: 4-10 x 10^9/L) was detected in 18 out of 33 patients (54.54%), primarily due to lymphocytosis.

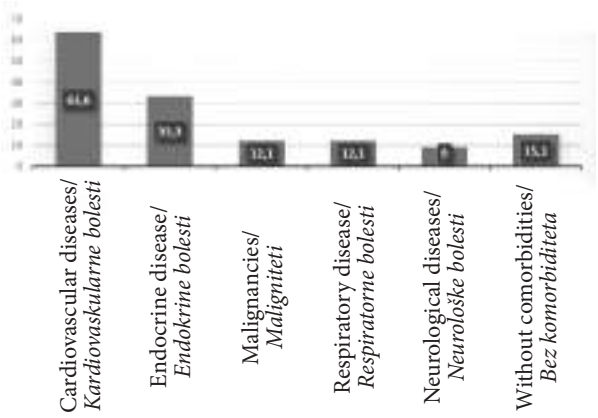
Among the predisposing factors contributing to disease onset, comorbidities were identified **(Graph 2).** Concurrent diseases were documented in 28 out of 33 patients (84.84%), while five patients presented without comorbidities (15.15%).

Predominant comorbidities included cardiovascular conditions (21 out of 28 patients – 63.6%), endocrine disorders (11 out of 28 patients – 33.3%), malignancies (4 out of 28 patients – 12.1%), respiratory conditions (4 out of 28 patients – 12.1%), and neurological disorders (3 out of 28 patients – 9%).

Antibiotic, antiviral, corticosteroid, antiedematous, and symptomatic therapies were continued until the causative agent was identified.

Out of the total number of patients treated at the UCCV Infectious Diseases Clinic during the examined year, 13 (39.4%) were transferred to the Intensive Care Unit due to respiratory complications, insufficient oxygenation, or altered consciousness leading to coma.

During the years 2021 and 2022, ten out of thirty-three patients (31.3%) treated at the UCCV Infectious Diseases Clinic experienced a fatal outcome.



Graph 2. Presence of comorbidities as one of the predisposing factors for the occurrence of WNV encephalitis
Grafikon 2. *Prisustvo komorbiditeta kao jednog od predisponirajućih faktora za nastanak virusa Zapadnog Nila encefalitisa*

Discussion

The WNV was first identified in the bloodstream of a febrile patient in Uganda in 1937. Subsequently, the virus spread progressively through migratory birds, originating from Africa and extending to other continents. Before 2004, WNV was associated with sporadic occurrences in humans and equines in Europe. Considering the favorable geographical conditions, appropriate climatic factors, the presence of vectors, and the rising incidence of cases along the Danube River, the first instances of WNV encephalitis occurred in our region [17].

The initial detection of WNV antibodies in clinically asymptomatic individuals in Serbia was documented in 1972, using inhibition and hemagglutination techniques. The first clinical epidemic of WNV infection in humans in the Republic of Serbia occurred in 2012. In 2013, the Republic of Serbia had the highest number of reported WNV infection cases among European countries, with 32 confirmed patients [18].

Considering the demographic profile of our nation, out of the 33 patients included in our study, 18 individuals (54.5%) reside in rural areas.

In contrast, during a 1996 epidemic in Romania, the highest infection rate was observed in districts adjacent to the Danube River, with 61% of patients residing in urban areas [19]. Conversely, during the 2010 epidemic in Greece, the affected population was predominantly from rural areas, although data on residence proximity to rivers were also considered [20].

Multiple European and American studies corroborate that over 90% of infections are attributed to the seasonal WNV, with the highest incidence rate occurring between July and September [11].

Both epidemic waves analyzed in our study pertain to the same period of complaints and hospitalizations, with August being the predominant month in both surveyed years.

In a study conducted in Romania, age and gender are identified as the primary predisposing factors for WNV infections. It has been noted that WNV infection is significantly more prevalent in the elderly population compared to younger individuals. During the 2010 epidemic in Romania, where WNV infection was confirmed in 50 cases, the average age of the patients was 59.5 years (ranging from 12 to 81 years). In our study, no confirmed cases were recorded in individuals below the age of 18 years, with an average age of 63 years (ranging from 38 to 83 years), predominantly comprising the geriatric population (17 out of 33 patients). In both studies, males constituted the majority, comprising 57.6% in our case and 68% in the Romanian study [21].

A 2020 American study reported similar findings, with 559 cases of neuroinvasive forms of WNV infection recorded. The incidence escalated with advancing age, with the highest number of patients falling in the age group over 65 years. Additionally, a higher frequency of infection was noted among males [22]. In Europe, specifically in Hungary, a study conducted in 2018 and 2019 revealed that out of a total of 183 confirmed cases of WNV infection, males were more frequently affected [23].

Several factors contribute to the variability in the clinical presentation of WNV neuroinvasive infection. These factors encompass age, the physiological condition of the affected host, viral strain, tropism, and virus pathogenesis. In our study, the primary symptom upon admission was elevated body temperature. Conversely, in a study conducted in Romania, headache predominated in addition to elevated temperature. The same study described maculopapular and erythematous petechial rashes, which were not observed in patients treated at the UCCV Infectious Diseases Clinic. Gastrointestinal symptoms were reported in patients in both studies. In our patients, nausea was predominantly observed in 42.2% of cases, while vomiting was noted in 45.5% [21].

Literature data suggest that susceptibility to infections, as well as the severity of the clinical presentation and treatment outcomes, are significantly influenced by comorbidities. They are acknowledged as prominent risk factors for patients with cardiovascular, endocrine, malignant, respiratory, and neurological disorders. In our study, five out of 33 patients had no comorbidities (15.1%), while cardiovascular diseases were the most prevalent (63.6%), consistent with an American study conducted in California from 2004 to 2017 [24].

The timely identification and management of complications, which may contribute to an unfavorable disease outcome, can substantially enhance prognosis. In the initial stages of infection, RT-PCR can serve as a valuable diagnostic procedure. Following seroconversion, the diagnosis is more reliably established through serological testing [23]. In our study, 31 out of 33 patients underwent RT-PCR testing, yielding positive results for the presence of the WNV genome in 9 patients (27.27%). This outcome may be attributed to inadequate sampling or patients presenting at a later stage of the disease. In a study by Aslan et al. conducted in 2012, no positive RT-PCR results were obtained for the WNV genome in a sample of 23 patients [25]. Serology serves as the cornerstone for confirming WNV infection, involving the detection of antibodies in serum or cerebrospinal fluid, often using ELISA for IgM or IgG [26]. Serological testing was conducted on all patients in our study, revealing positive IgM antibodies in serum or cerebrospinal fluid in 78.8% of cases. The obtained data align with studies conducted in 2012 at the UCCV Infectious Diseases Clinic, as well as the Clinics for Tropical and Infectious Diseases of the Clinical Center of Serbia [18, 27]. Numerous European authors emphasize the significance of serological diagnostics in confirming the definitive diagnosis and determining the etiology of the infection [26–28].

In 2018, the largest outbreak ever documented, attributable to WNV, occurred in Central and Southern Europe, resulting in over 2000 symptomatic cases in humans, predominantly reported in Italy, with a mortality rate of approximately 9% [23]. In our country, within the territory of the Autonomous Province of Vojvodina, during the 2012 epidemic, 32 cases of WNV encephalitis were documented with a mortality rate of 3.13% [18]. In contrast, in our study comprising a total of 33 registered patients, the mortality rate was 31.3%. This difference could be attributed to the average age of patients in our study, where the geriatric population predominated, compared to the 2012 study, which included predominantly working–age individuals. Furthermore, comorbidities were documented in as many as 84% of our patients, contrasting with the study by Sević S. et al., where accompanying diseases were registered in 37.5% of the total number of patients included in the mentioned study.

Conclusion

For neuroinvasive infections, the Enzyme-linked Immunosorbent Assay test has proven to be the most reliable diagnostic method during both epidemic years. Research has confirmed that the geriatric population is at a heightened risk of contracting the neuroinvasive form of West Nile Virus infection. Additionally, the presence of comorbidities, particularly cardiovascular disease, significantly influences the

severity of clinical presentation, the duration of hospitalization, and the disease outcome. Epidemiologically, it has been verified that West Nile Virus infection is most commonly observed during the summer months in areas situated near large bodies of flowing water. The findings emphasize the importance of ongoing community efforts aimed at eradicating mosquito species in the Danube region and other waterways of Vojvodina.

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ASPECTS OF MOTOR FUNCTIONING OF BLIND AND VISUALLY IMPAIRED CHILDREN – THE IMPORTANCE OF SOMATOPEDIC TREATMENT

ASPEKTI MOTORIČKOG FUNKCIONISANJA SLEPOG I SLABOVIDOG DETETA – ZNAČAJ SOMATOPEDSKOG TRETMANA

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Summary

Introduction. Given that vision significantly influences motor function, particularly in the execution of voluntary movements, this study aimed to determine whether targeted somatopedic training could enhance certain motor aspects in visually impaired children. The study focuses on the following components: coordination, balance, manipulative dexterity, and walking. **Material and Methods.** The sample comprised 60 children from three schools: the Primary School for Vision Protection "Dragan Kovačević" in Belgrade, the School for Visually Impaired Children "Veljko Ramadanović" in Zemun, and the Elementary School "Djordje Krstić" in Belgrade. The experimental group included children aged 6-15 years with visual impairments, average intellectual abilities, and normal neurological and psychological status. The control group was matched by number, gender, and age, consisting of students from regular schools. We assessed motor functioning using tests for hand manipulative skills, coordination of upper and lower extremities, and body balance while walking and standing. **Results.** Statistically significant differences were observed between the experimental and control groups in all examined subtests: manipulative dexterity (p=0.006); coordination of upper extremities (p=0.029); coordination of upper and lower extremities (p=0.005); maintaining balance during walking (p=0.002); maintaining balance while standing (p=0.024), and walking (p=0.010). **Conclusion.** The results clearly indicate the importance of somatopedic treatment in improving motor functions of blind and visually impaired children.

Key words: Blindness; Visually Impaired Persons; Psychomotor Performance; Motor Skills; Postural Balance; Walking; Child Development

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Sažetak

Uvod. Imajući u vidu da čulo vida u velikoj meri determiniše motoričko funkcionisanje, naročito u kontroli izvršenja voljnog pokreta, želeli smo da utvrdimo da li se ciljanim somatopedskim treningom mogu popraviti neki motorički aspekti kod dece oštećenog vida. Odabrane komponente činili su: koordinacija, ravnoteža, manipulativna spretnost i hod. **Materijal i metode.** Uzorak je obuhvatao 60 dece iz Osnovne škole za zaštitu vida „Dragan Kovačević" u Beogradu, Škole za decu oštećenog vida „Veljko Ramadanović" u Zemunu i Osnovne škole „Đorđe Krstić" u Beogradu. Eksperimentalnu grupu činila su deca uzrasta 6−15 godina sa oštećenjem vida, prosečnim intelektualnim sposobnostima i urednim neurološkim i psihološkim statusom. Kontrolna grupa je bila ujednačena po broju, polu i uzrastu sa eksperimentalnom grupom i sastojala se od učenika iz redovne škole. Za procenu motoričkih funkcija koristili smo testove za manipulativne veštine ruku, koordinaciju pokreta gornjih i donjih ekstremiteta, kao i održavanje ravnoteže tela pri hodu i stajanju. **Rezultati**. Prisustvo statistički značajnih razlika među eksperimentalne i kontrolne grupe, utvrđeno je na svim ispitivanim suptestovima: manipulativna spretnost (p = 0,006); koordinacija pokreta gornjih ekstremiteta (p = 0,029); koordinacija pokreta gornjih i donjih ekstremiteta (p = 0,005); održavanje ravnoteže tela pri hodu (p = 0,002); održavanje ravnoteže tela pri stajanju (p = 0,024) i hoda (p = 0,010). **Zaključak.** Dobijeni rezultati nedvosmisleno ukazuju na značaj somatopedskog tretmana u poboljšanju motoričkog funkcionisanja slepe i slabovide dece.

Ključne reči: slepilo; slabovide osobe; psihomotorne performanse; motoričke sposobnosti; posturalni balans; hodanje; razvoj deteta

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Introduction

In the field of science, patient care, and treatment the primary principles guide us to focus on the patient rather than the diagnosis, adhering to the rule "first, do no harm" [1]. Analyzing the motor functioning of blind and visually impaired children is particularly challenging due to its critical role in their overall psychophysical development. Common misconception is that motor functioning is simple in its structure and function. However, a deeper analysis, grounded on a scientific methodology, reveals inherent complexity. Research

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indicates that motor function cannot be regarded as a singular ability; instead, it comprises several broad groups of specific abilities, whose boundaries are not clearly underlined.

Motor development in children involves the gradual acquisition of muscle control. This development results from the maturation of neural structures, bones, and muscles, as well as changes in body proportions. Additionally, learning opportunities enable the coordinated use of various muscle groups. The structure of motor functioning provides a fundamental basis for expanding knowledge and gaining new experiences. At the core of motor development is a hierarchy involving the maturation of innate anatomical and physiological systems.

The locomotion of a newborn is immature. The central nervous system, locomotor apparatus, sensory organs, and other body systems develop throughout childhood. During this time, a child learns and adopts new motor patterns, which become automated and more complex over time. This development follows genetically established patterns and is stimulated by environmental stimuli. Concurrently, intellectual abilities develop, collectively shaping an individual's life potential. Each system involved in this development plays a crucial role, and it is difficult to prioritize their importance. These systems are interdependent, and any inadequacy or absence of one factor can impede the harmonious development of other abilities.

Visual perception is a fundamental human cognitive function, playing a dominant and integrative role in the perception process. Approximately 90% of information from the external environment is perceived through vision. Vision helps humans understand the basic features of their surroundings, including color, size, shape, and spatial relationships such as distance, direction, and movement. Through vision, individuals learn imitation, self-awareness, and social behavior, facilitating adequate social interactions. Cognitive sensory perception relies on the interplay between various systems, forming complex dynamic connections among visual-tactile, visual-auditory, and visual-motor systems. Moreover, vision enhances the quality to other sensory information. These connections underpin the motor, emotional and intellectual functioning of an individual.

Motor development of visually impaired children

In his research, "Preschool Children with Visual Impairments", Bishop [2] asserts that developmental norms are based on observations of children with normal sight. Bishop notes that only a few studies support direct comparison between blind children and those with normal vision. Current research suggests that blind children follow their own specific laws of motor development. What might appear as a "delay" is, in fact, a normal developmental course for a blind child. The specific developmental laws for blind children are not well-defined, partially due to their relatively low population and the lack of comprehensive regional and national databases. Until these norms are established, blind children will continue to be compared to sighted children, leading to the identification of "delays".

Bishop highlights that the most noticeable delays in visually impaired children are in motor development. Vision serves as a primary motivator for many motor activities (e.g., head control, upright posture, reaching, and locomotion), which may be absent in blind children. However, early interventions can often minimize these delays. Additionally, hearing is not as strong motivator for initiating movements such as catching and grabbing. "Catching by sound" is not equivalent to "catching by visual stimulus", so delay in locomotion due to auditory cues cannot be fully compensated, as auditory development does not offer the same adaptive advantages as visual development. When vision is substituted with hearing or touch as stimuli, it is important to remember that touch and hearing are sequential, not continuously like vision. Key developmental milestones, such as head control, independent sitting, arm and hand use, crawling, standing, and walking, are delayed without additional stimulation, typically by several months.

Udo and Fils [3] found significant delays in the use of hands in blind children, even though their arms and hands are primary organs of perception.. At five months, a blind child might keep closed fists at a shoulders level. There will be no touching of fingers of both hands, and they will not be active in the medial line. In this age, a sighted child is already practicing coordinated movements and moving an object from one hand to the other. This delay impacts both gross and fine motor skills, as the absence of vision prevents the natural coordination of hands and eyes. Instead, blind children must rely on ear–hand coordination, which requires more experience and develops later than eye–hand coordination. Without attempting to reach for sound sources by around 12 months, blind children will not explore their environment through crawling or walking.

The inability to perceive and imitate movement, combined with the lack of self-confidence and inhibition, affect walking development in blind children. Motor visual imitation is crucial for learning to walk, expressing vocal movements, engaging in various games, and performing daily activities. Without visual imitation, blind children's locomotion is significantly poorer. They rely on tactile-kinesthetic imitation, learning through passive tactile guidance [4].

Walking is a source of enjoyment for both blind and sighted children. While sighted children learn to balance after a few weeks, blind children require more time. Once they achieve an upright position and balance, further development can occur. Understanding body control (a child's perception of their capabilities and awareness that others have similar abilities) and space recognition (realizing that there is space "right outside") involves cognitive abilities. When this understanding is reached, coordinated and purposeful movements within the environment can occur, facilitating interactions and orientation within their world [2]. Blind children's walking has

certain characteristics: a nearly motionless upper body, limited arm swinging, a forward-inclined head, and widely spread feet in a fan-shaped form [4].

Fine motor skills also develop more slowly in visually impaired children. Vision aids in controlling, imitating and refining these movements. Blind children find it challenging to acquire grasping movements (e.g., the use of accessories, crayons…) and "academic skills" like stacking cubes, coloring, coating, and using scissors [5].

Jablan [6] found that in a sample of 95 blind and practically blind primary school children, 55.8% showed harmonious motor development. Minimal difficulties were noted in praxis activities, oral motor functions, and differentiation of motor functions of fingers and hands. However, tasks requiring physical integrity experience and kinetic movements were moderately challenging. The least developed motor function was motor preservation. The research results indicate slower motor functions development in blind children due to the lack of visual experience, sensory and motor deficits, and poor experiential foundations.

In the study "Motor skill performance of school-age children with visual impairments" [7] researchers explored different motor achievements in visually impaired children aged 7–10 years using the MABC test battery. The analysis showed that children with visual impairments performed slower in hand usage tests compared to sighted children, regardless of compensatory skills (reducing the distance and using proprioceptive information) or regardless of severity of visual impairment. Significant difficulties were observed in eye-hand coordination tasks, with the greatest difference found in bimanual coordination test. No statistically significant difference was found in dynamic balance, but there was a difference in static balance. The authors concluded that the poorer results in the experimental group were solely due to visual impairments.

Jablan, Vučinić, and Gligorović [8] investigated motor function development, spatial orientation, and the relationship between these aspects in blind primary school children. They found motor function difficulties in 44.2% of participants, with motor abilities improving with age. A positive correlation was also found between intellectual abilities, motor functions, and school achievement.

Brambring [9] describes three theoretical interpretations of delayed motor development in blind children. One theory links delays directly to the primary deficit, i.e., the lack of vision, which prevents or restricts a blind child to gain adequate experience in a social environment that can be reached by motor activities under physiological conditions. Another theory attributes delays to a non-stimulating social environment and low expectations. The third theory suggests that delays are due to various adaptive compensation mechanisms, where different effective alternative strategies can help blind children compensate for their primary deficit to varying degrees.

In the previous discussion, we established that children with visual impairment face significant challenges in motor functioning, impacting their daily lives. Our study specifically aimed to investigate whether targeted somatopedic training could improve certain motor aspects in visually impaired children. The selected components included manipulative dexterity, coordination, balance, and walking, which served as the dependent variables in our study. The independent variables included the level of visual impairment, gender, age, and the treatment applied. By examining these variables, we aimed to determine the effectiveness of somatopedic training in enhancing the motor functions of visually impaired children.

Material and Methods

The study sample consisted of 60 children selected from three schools: the Primary School for Vision Protection "Dragan Kovačević" in Belgrade, School for Visually Impaired Children "Veljko Ramadanović" in Zemun, and Primary School "Djordje Krstić" in Belgrade. The inclusion criteria were as follows: visual impairment defined according to the World Health Organization standards, age of the participants ranging from 6-15 years, encompassing both younger and older primary school students, children with average intellectual abilities as determined by their inclusion in regular curriculum classes during school enrollment, and normal neurological and psychological statuses to avoid the confounding effect on motor abilities. The sample was divided into two groups: Experimental Group (E), consisting of 30 children (15 blind and 15 visually impaired) who received targeted somatopedic treatment, and Control Group (K), consisting of 30 children (15 blind and 15 visually impaired) who did not receive somatopedic treatment.

The somatopedic treatment was conducted by special education and rehabilitation teacher, based on individualized and group somatopedic programs. The research lasted for twelve weeks, during which the Group E children underwent somatopedic treatment.

To gather the required data and achieve the study's objectives, we employed the following methods and instruments: analysis of school ophthalmological documentation, analysis of school pedagogical-psychological documentation, analysis of medical records, and special education and rehabilitation tests. By examining the school ophthalmological documentation, we obtained information on the level and type of visual impairment. Visual acuity, whether at the low vision level or at the blindness level, was assessed according to the World Health Organization's definition. Given the upper limit of low vision provides some flexibility in terms of visual acuity, it was essential for the information to be documented by the Commission for Classification and Categorization of the Republic of Serbia. Data on the participants' gender, school age, and academic performance were gathered from the school pedagogical-psychological documentation. We obtained information on birth date, presence of other illnesses, the age at which the child began walking, early childhood motor development, and medical interventions related to vision from the medical

records of school health records. Children with neurological impairments and children whose intellectual abilities indicated developmental delays were excluded from the research. Consequently, we used the following special education and rehabilitation tests: Test for assessing manipulative dexterity of the hand (Task I according to Lafaye) [9]; Test for assessing movement coordination of the upper extremities [11]; Test for assessing movement coordination of the upper and lower extremities [10]; Test for assessing balance maintenance during walking [12]; Test for assessing balance maintenance when standing [12]; Test for assessing gait [11].

Descriptive statistical methods were used to process the collected data, including percentages, means, and standard deviations, while ANOVA model, correlation analysis and t-test were employed to determine the correlation between dependent and independent variables.

Results

The assessment of participants' achievements and performance was conducted before and after treatment, as detailed below (**Table 1**).

Initially, both the E and K groups showed similar levels of performance based on the number of strung beads, as illustrated in the combined table above. However, following treatment, a notable increase in the number of "very successful" participants was observed in the E group compared to the K group. Specifically, the proportion of "very successful" participants in the E group increased from 21 (63.6%) to 9 (30%), while in the K group, it increased from 12 (40%) to 21 (63.6%).

Furthermore, after treatment, no participants in the E group were classified as "unsuccessful", whereas in the K group, this proportion increased from 0% to 13.3%. The number of participants classified as "successful" decreased in both groups, with 14 (46.7%) in the K group and 9 (30%) in the E group, as more participants transitioned to the "very successful" category after treatment.

Statistical analysis revealed a significant difference in performances between the E and K groups after treatment ($p=0.006$, $r=0.350$), indicating the effectiveness of the treatment intervention.

Regarding the evaluation results from the Lafaye test, participants were categorized based on the number of adverse movements during both measurements. Notably, after the first measurement, there was no statistically significant difference between the E and K groups. However, after treatment, the E group demonstrated significantly fewer adverse movements during task execution compared to the K group ($p=0.015$; $r=0.314$).

Overall, these findings underscore the effectiveness of the treatment intervention, particularly in enhancing performance and reducing adverse movements within the E group relative to the K group.

Table 2 presents a comparative analysis of successful task performance between groups E and K before and after treatment intervention.

Before treatment, both groups exhibited similar levels of successful task completion, with the majority of participants in the "task completed successfully" category. Specifically, 55% of participants in both groups successfully completed the task during the initial assessment, while none were categorized as "unsuccessful". However, noticeable differences emerged after the second assessment.

In group E, the proportion of participants in the "task completed successfully" category increased substantially to 80%, accompanied by a decrease in the proportion categorized as having "problems in task performance" (B category). Conversely, in group K, although there was a slight increase in successful task completion (53.3% from 55%), the change was minimal compared to group E. Statistical analysis revealed a significant difference between the two groups after the treatment intervention ($p=0.029$, $r=0.283$).

Before treatment, both groups demonstrated comparable levels of successful task performance, with no statistically significant difference between them ($p>0.05$). The distribution of participants across categories ("unsuccessful", "problem in task performance", and "task completed successfully") was fairly equal,

Table 1. Achievements of participants in relation to performance/number of stringing beads and number of adverse movements on Lafaye test

Tabela 1. *Postignuća ispitanika u odnosu na uspešnost/broj nizanja perli i nuskretnji na Lafaj testu*

Group *Grupa*	I Measurement/*Merenja*			II Measurement/*Merenja*				
	*A	*B	*V	*A	*B	*V	*GI	*GII
E	2 (6.7%)	15 (50%)	13 (43.3%)	0	9 (30%)	21 (63.6%)		
E	1 (3.3%)	1 (3.3%)	15 (50%)	0	1 (3.3)	9 (30%)	13 (43.3%)	20 (66.7%)
K	5 (16.7%)	15 (50%)	10 (33.3%)	4 (13.3%)	14 (46.7%)	12 (40%)		
K	1 (3.3%)	3 (10%)	18 (60%)	1 (3.3%)	3 (10%)	15 (50%)	8 (26.7%)	11 (36.7%)
Total/*Ukupno*	7 (11.7%)	30 (50%)	23 (38.3%)	4 (6.7%)	23 (38.3%)	33 (55%)		
Total/*Ukupno*	2 (3.3%)	4 (6.7%)	33 (55%)	1 (1.7%)	4 (6.7%)	24 (40%)	21 (35%)	31 (51.7%)

Legend: *A – unsuccessful; *B – successful; *V – very successful
Legend: *A – unsuccessful; *B – 3 to 5 mistakes; *V – 1 to 2 mistakes; *G – no mistakes
*Legenda: *A – neuspešni; *B – uspešni; *V – veoma uspešni*
*Legenda: *A – neuspešni; *B – 3 do 5 grešaka; *V – 1 do 2 greške; *G – bez greške*

Table 2. Achievements of participants in relation to coordination of upper extremities and of upper and lower extremities
Tabela 2*. Postignuća ispitanika u odnosu na koordinaciju gornjih ekstremiteta i gornjih i donjih ekstremiteta*

	I Measurement/*Merenja*			II Measurement/*Merenja*		
Group/*Grupa*	*A	*B	*V	*A	*B	*V
E	0	12 (40%)	18 (60%)	0	6 (20%)	24 (80%)
E	2 (6.7%)	13 (43.3%)	15 (50%)	0	6 (20%)	24 (80%)
K	0	15 (50%)	15 (50%)	0	14 (46.7%)	16 (53.3%)
K	4 (13.3%)	14 (46.7%)	12 (40%)	2 (6.7%)	14 (46.7%)	14 (46.7%)
Total/*Ukupno*	0	27 (45%)	33 (55%)	0	20 (33.3%)	40 (66.7%)
Total/*Ukupno*	6 (10%)	27 (45%)	27 (45%)	2 (3.3)	20 (33.3%)	38 (63.3%)

Legend: *A – unsuccessful; *B – problem in task performance; *V – task completed successfully
*Legenda: *A – neuspešni; *B – problem u izvođenju zadatka; *V – uspešno izveden zadatak*

Table 3. Achievements of participants in relation to dynamic balance and static balance
Tabela 3. *Postignuća ispitanika u odnosu na dinamičku ravnotežu i na statičku ravnotežu*

	I Measurement/*Merenja*			II Measurement/*Merenja*		
Group/*Grupa*	*A	*B	*V	*A	*B	*V
E	6 (20%)	13 (43.3%)	11 (36.7)	2 (6.7%)	5 (16.7%)	23 (76.7%)
E	5 (16.7%)	22 (73.7%)	3 (10%)	2 (6.7%)	10 (33.3%)	18 (60%)
K	5 (16.7%)	18 (60%)	7 (23.3%)	3 (10%)	18 (60%)	9 (30%)
K	8 (26.7%)	19 (63.3%)	3 (10%)	3 (10%)	19 (63.3%)	8 (26.7%)
Total/*Ukupno*	11 18.3%)	31 (51.7%)	18 (30%)	5 (8.3%)	23 (38.3%)	32 (53.3%)
Total/*Ukupno*	13 21.7%)	41 (68.3%)	6 (10%)	5 (8.3%)	29 (48.3%)	26 (43.3%)

Legend: *A – unsuccessful; *B – problem in task performance; *V – task completed successfully
Legend: *A – unsuccessful; *B – with certain problems; *V – in accordance with the requirement
*Legenda: *A – neuspešni; *B – problem u izvođenju zadatka; *V – uspešno izveden zadatak*
*Legenda: *A – neuspešni; *B – uz određeni problem; *V – u skladu sa zahtevom*

with the lowest percentage in the "unsuccessful" category (10%). However, notable variations were observed after treatment.

In group E, there were no participants classified as "unsuccessful" after treatment, with a substantial increase to 80% of participants successfully completing the task. In contrast, in group K, although there was a marginal increase in successful task completion (46.7% from 45%), the number of participants facing "problems in task performance" remained unchanged. Statistical analysis indicated a significant difference between the two groups after treatment intervention (p=0.005, r=0.361).

Overall, the results highlight the effectiveness of the somatopedic treatment, particularly evident in group E, where a higher proportion of participants achieved successful task completion following intervention compared to group K.

Table 3 presents a comparative assessment of task performance between groups E and K before and after treatment intervention.

Initially, both groups demonstrated similar levels of task execution, with the majority of participants falling into the "problem in task performance" category (B category). Specifically, 51.7% of participants from both groups encountered some difficulties in task execution, while a smaller proportion was categorized as "unsuccessful" (20% in E group and 16.7% in K group).

Following the treatment intervention, significant improvements were observed in group E. A substantial 76.7% of participants from group E successfully completed the task (V category), compared to only 30% in group K. Conversely, in group K, the majority of participants (60%) remained in the "problem in task performance" category, with only 16.7% achieving successful task completion. This shift in performance led to a statistically significant difference between the two groups post-treatment (p=0.002, r=0.388).

Additionally, before treatment, both groups exhibited comparable distributions across task performance categories, primarily in the "problem in task performance" category (68.3% in each group). However, a slightly higher percentage of participants in group K were unsuccessful in task execution (26.7%). Subsequent to treatment, marked improvements were evident in group E, with 60% of participants achieving successful task completion, compared to 26.7% in group K. The majority of participants in group K (63.3%) continued to face challenges in task execution, remaining in the "problem in task performance" category. This disparity in performance post-treatment resulted in a statistically significant difference between the groups (p=0.024, r=0.292).

In summary, the findings underscore the efficacy of the treatment intervention, particularly in enhancing task performance among participants in group E compared to group K.

In Table 4, initial testing revealed that both E and K groups had 60% of participants in the "problem in

Table 4. Achievements of participants in relation to walking assessment
Tabela 4. *Postignuća ispitanika u odnosu na procenu hoda*

	I Measurement/*Merenja*			II Measurement/*Merenja*		
Group/*Grupa*	*A	*B	*V	*A	*B	*V
E	1 (3.3%)	18 (60%)	11 (36.7%)	0	12 (40%)	18 (60%)
K	3 (10%)	18 (60%)	9 (30%)	2 (6.7%)	19 (63.3%)	9 (30%)
Total/*Ukupno*	4 (6.7%)	36 (60%)	20 (33.3%)	2 (3.3%)	31 (51.7%)	27 (45%)

Legend: *A – 5 and more poor walking characteristics *B – 2 to 4 poor walking characteristics *V – walks well
*Legenda: *A – 5 i više loših karakteristika hoda *B – 2 do 4 loše karakteristike hoda *V – dobro hoda*

Table 5. Analysis of the results of the E group using a t-test after the first and second testing of dependent variables
Tabela 5. *Analiza dobijenih rezultata E grupe nakon prvog i drugog testiranja zavisnih varijabli primenom t-testa*

Testing 1 and 2/*Proba 1 i 2*	t	df	Sig
Lafaye 1 testing 1/*Lafaye 1 proba 1*	-3.07	29	.005
Lafaye 1 testing 2/*Lafaye 1 proba 2*	-3.53	29	.001
Coordination of upper extremities testing 1/*Koordinacija gornjih ekstremiteta proba 1* Coordination of upper extremities testing 2/*Koordinacija gornjih ekstremiteta proba 2*	-2.69	29	.012
Coordination of *U and*L extremities testing 1/*Koordinacija *G i *D ekstremiteta proba 1* Coordination of *U and*L extremities testing 2/*Koordinacija *G i *D ekstremiteta proba 2*	-4.09	29	.000
Dynamic balance testing 1/*Dinamička ravnoteža proba 1* Dynamic balance testing 2/*Dinamička ravnoteža proba 2*	-5.76	29	.000
Static balance testing 1/*Statička ravnoteža proba 1* Static balance testing 2/*Statička ravnoteža proba 2*	-6.59	29	.000
Walk testing 1/*Hod broba 1* Walk testing 2/*Hod proba 2*	-3.25	29	.003

Legend: *U – upper extremities; *L – lower extremities
*Legenda: *G – gornji ekstremiteti; *D – donji ekstremiteti*

task performing" (B) category, with E group showing slightly better walking proficiency (36.7%). No significant difference existed between the groups initially. After treatment, significant improvements were observed in the E group, with no participants in the "unsuccessful" (A) category and 60% in the "walks well" (V) category. In comparison, the K group had only 30% of participants in the "walks well" (V) category, with one participant shifting. A statistically significant difference emerged during the second testing (p=0.010, r=0.329), indicating varied treatment impact on task performance between groups. **Table 5** confirms that the quality of performance significantly improved following somatopedic treatment.

Discussion

Manipulative dexterity begins developing in infancy, becoming most prominent during preschool years but continuing throughout childhood. This skill is crucial for everyday tasks, from basic physiological activities to more complex tasks like writing and drawing, which are essential for social functioning. For children with impaired vision, particularly blind children, manipulative dexterity is even more vital. They heavily rely on their hands for gathering information, reading, and writing, providing invaluable sensory input that cannot be obtained through other means. Thus, our research aimed to assess manipulative dexterity in children with impaired vision and evaluate the effectiveness of targeted somatopedic treatment.

We assessed manipulative dexterity using the Lafaye test, evaluating participants' ability to string beads. We categorized participants based on the number of beads strung: those who strung between 9-25 beads were deemed "successful", those who strung more than 25 beads were categorized as "very successful", and those who strung fewer than 9 beads were labeled "unsuccessful". The results are presented in **Table 1.**

Initially, most participants from both E and K groups fell into the "successful" category (50%), followed by "very successful" (38.3%), with the fewest classified as "unsuccessful" (11.7%). There was no significant difference between the E and K groups during the first measurement. However, post-treatment, significant differences emerged. In the E group, there were no "unsuccessful" participants, with the number of "successful" participants decreasing to 30% and "very successful" increasing to 63.6%. This disparity between group performances was statistically significant during the second measurement (p=0.006, r=0.350), indicating that somatopedic treatment effectively improved manipulative dexterity.

Researchers investigating the coordination abilities of visually impaired children noted difficulties in expressing these motor skills. Zemcova [13] observed that children with low vision often exhibit deficits in coordination, while Nikolic et al. [14] found that coordination issues were prevalent in 54.4% of such children, among other signs of developmental delay.

In our study, as shown in **Table 2**, none of the participants in either the E group or the K group failed the task during the initial measurement. The percentage of participants encountering difficulty in task execution was 45%, with 55% successfully completing it. There was no statistically significant difference between the groups at this stage.

During the second measurement, we observed that there were still no unsuccessful participants. However, the percentage of successful task completion increased to 80% in the E group and 53.3% in the K group. Statistical analysis revealed a significant difference between these two groups after treatment application, with a p-value of 0.029 and a correlation coefficient of r=0.283.

It's noteworthy that there were no unsuccessful participants in either measurement. This suggests that the task may have been relatively easy for participants at this level of coordination ability testing.

Upon reviewing **Table 2,** we observed that 50% of participants in the E group successfully completed the task during the initial measurement, while 43.3% encountered difficulties, and only 6.7% were unsuccessful. In contrast, in the K group, 13.3% were unsuccessful, 40% succeeded, and 46.7% faced challenges in task performance. Following the second testing, no participants in the E group were unsuccessful, with 80% successfully completing the task. Subsequent to treatment, the E group exhibited significantly improved results, with a statistically significant difference noted (p=0.005, r=0.361).

Balance constitutes a fundamental motor skill, serving as the basis for various motor functions alongside coordination. Its full development is crucial for sitting, walking, and other motor activities. While genetic factors play a role in its development, sensory stimuli are also essential, particularly for children with impaired vision. **Table 3** illustrates the distribution of participants from both groups concerning dynamic balance, specifically walking. Initially, 20% of E group participants were unsuccessful, 43.3% encountered difficulties, and 36.7% succeeded. In the K group, 16.7% were unsuccessful, 23.3% succeeded, and 60% faced challenges. Initially, both groups showed similar achievements without statistical significance. Post-treatment, 76.7% of E group participants succeeded, with only 6.7% unsuccessful, while K group participants showed slight improvement, resulting in a statistically significant difference (p=0.002, r=0.388). This underscores the substantial impact of somatopedic treatment on enhancing dynamic balance, emphasizing its susceptibility to practice.

Table 3 illustrates the distribution of participants from both the E and K groups during the initial and subsequent measurements concerning static balance when standing. In the E group, 16.7% were unsuccessful, 73.7% completed the task with some difficulty, and only 10% completed it as requested. Similarly, in the K group, only 10% completed the task as requested, while 26.7% were unsuccessful. Initially, both groups showed similar achievements, with no statistically significant difference noted.

Following treatment in the E group, the percentage of participants completing the task as requested increased to 60%, with 6.7% being unsuccessful. The percentage of participants encountering specific difficulties remained unchanged (63.3%), while the percentage of unsuccessful attempts decreased to 10% in the K group. Although a statistically significant difference was found between the achievements of participants from the E and K groups during the second measurement (p=0.024, r=0.292), it is evident that better outcomes were attained through normal biological maturation and development in the K group.

Walking is a fundamental human activity enjoyed by both sighted and blind children. However, certain prerequisites such as coordination, balance, and body posture are necessary for appropriate walking development. It has been observed that blind children exhibit specific characteristics during walking, including minimal upper body movement, limited arm swinging, forward head inclination, and a fan-shaped foot placement. Furthermore, posture disorders, gait abnormalities, and physical deformities are common in children with impaired vision, often manifesting as downward head posture, rounded shoulders, sunken chest, convex abdomen, and spinal curvature.

In our research, walking was assessed as a dependent variable based on known characteristics. **Table 4** indicates that during the initial measurement, 3.3% of participants in the E group exhibited five or more poor walking characteristics, compared to 10% in the K group. The majority of participants (60%) in both groups displayed 2 to 4 poor walking characteristics, while 36.7% in the E group and 30% in the K group were categorized as having a good walk. There was no statistically significant difference between the groups due to even distribution.

Following treatment, a significant reduction in poor walking characteristics was observed among E group participants. No participants in the E group exhibited five or more poor characteristics, whereas 6.7% did so in the K group. Additionally, 60% of E group participants demonstrated a good walk post-treatment, compared to 30% in the K group. Notably, the highest percentage of E group participants exhibited a good walk, while the highest percentage of K group participants fell into the category of 2 to 4 poor walking characteristics (63.3%). A statistically significant difference between the groups was observed after the second measurement (p=0.010), with a correlation coefficient of r=0.329. This analysis suggests that somatopedic treatment positively impacted the characteristics of walking among blind and visually impaired participants, reducing the number of poor characteristics.

To verify the obtained results, a t-test was conducted to determine if there were differences within the E group after treatment. The correlation analysis revealed that the E group significantly differed from the K group after somatopedic treatment. To address concerns regarding potential regression in the K group and stagnation in the E group, an additional t-test was performed.

Conclusion

Our study reveals a significant presence of motor functioning difficulties among children with visual impairments, aligning with findings from previous research in this domain. However, our results underscore the potential for significant improvement in various aspects of motor functioning through timely intervention and targeted training.

These findings provide valuable insights for practitioners in designing targeted training and rehabilitation programs tailored to the needs of this population. Emphasizing early detection and intervention is crucial, highlighting the importance of initiating somatopedic treatment at the earliest age possible.

By prioritizing early intervention and implementing tailored programs, we can enhance the motor functioning outcomes and overall well-being of children with visual impairments, ultimately fostering their optimal development and quality of life. The results of this research can also serve as a foundation for other more extensive and comprehensive studies on this topic.

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CHILDBIRTH IN ADOLESCENTS – FEATURES AND OUTCOMES

POROĐAJI ADOLESCENTKINJA – KARAKTERISTIKE I ISHODI

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Summary

Introduction. Adolescent pregnancies significantly impact the welfare of young mothers, their infants, and the general population. These pregnancies represent a public healthcare concern associated with numerous consequences. **Aim**: To investigate the prevalence of adolescent pregnancies and their outcomes. **Material and Methods.** This retrospective descriptive study included adolescents who gave birth at the Gynecology and Obstetrics Clinic between January 1, 2020 and December 31, 2020. Data on anthropometric measurements, number and mode of deliveries, newborn birth weights, and complications were collected from medical records and statistically analyzed. **Results.** A total of 174 adolescents (aged 13-19) were included in the study. Most were first-time mothers living in common-law unions. Four spontaneous twin pregnancies were documented. No significant differences were found in the anthropometric measures between younger (<15 years old) and older (16-19 years old) adolescents. Pelvic measurements did not affect the mode of delivery. Younger adolescents and those with smaller pelvic measurements experienced longer hospitalizations. Vaginal delivery was the prominent mode of birth. Newborns delivered by caesarian section had significantly lower birth weights and lengths. While no significant complications during labor and delivery were observed, there was notable postpartum blood loss and higher rates of anemia in the puerperium. **Conclusion.** Although the number of adolescent pregnancies and births is declining, it still remains a significant concern. Well-developed perinatal care and the promotion of reproductive health within educational and health systems could not only further reduce pregnancy rates but also ensure optimal conditions for normal pregnancies and deliveries in adolescents.

Key words: Pregnancy in Adolescence; Adolescent; Pregnancy Outcome; Delivery, Obstetric; Cesarean Section; Infant, Newborn

Sažetak

Uvod. Trudnoće u adolescentnom periodu utiču na dobrobit mladih majki, njihovih beba i opšte populacije. One predstavljaju globalni javnozdravstveni problem povezan sa višestrukim posledicama. Cilj rada je da se izvrši uvid u prevalenciju trudnoća i ishode porođaja adolescentkinja, kao i njihove novorođenčadi. **Materijal i metode.** Retrospektivna, deskriptivna studija adolescentnih majki koje su porođene u periodu od 1. januara 2020. do 31. decembra 2020. godine na Klinici za ginekologiju i akušerstvo. Antropometrijski parametri, broj i način porođaja, težina novorođenčeta i podaci o komplikacijama povezanim sa trudnoćom i porođajem prikupljeni su iz medicinske dokumentacije i statistički analizirani. **Rezultati.** Ukupno je bilo 174 adolescentkinje (13−19 godina). Većina njih su bile prvorotke iz vanbračne zajednice. Verifikovane su četiri spontane blizanačke trudnoće. Nije bilo razlike u antropometrijskim merama mlađih (< 15 godina) i starijih (16−19) adolescentkinja. Karlične mere nisu uticale na način porođaja, ali je duži period hospitalizacije primećen kod mlađih adolescentkinja i onih sa manjim karličnim merama. Porođaj je uglavnom završen vaginalno. Utvrđeno je da su carskim rezom rođena deca sa značajno manjom telesnom masom i dužinom. Nisu verifikovane značajnije komplikacije, sporadično je uočen veći postpartalni gubitak krvi, kao i pacijentkinje sa anemijom u puerperijumu. **Zaključak.** Broj trudnoća i porođaja u adolescentnom uzrastu je u padu, ali i dalje predstavlja veliki problem i rizik. Adekvatno razvijena antenatalna i perinatalna zaštita i promocija reproduktivnog zdravlja u okviru obrazovnog i zdravstvenog sistema bi dovela do daljeg pada stope trudnoća, ali i obezbedila optimalne uslove za uredan tok trudnoće i porođaja adolescentkinja.

Ključne reči: adolescentska trudnoća; adolescenti; ishod trudnoće; prirodni porođaj; carski rez; novorođenče

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Abbreviations

OBGYN – Clinic for Gynecology and Obstetrics
UCCV – University Clinical Center of Vojvodina
MIN – the lowest/minimum value
MAX – the greatest/maximum value
VS. – Versus
MODE – modal value
USA – United States of America

Introduction

In recent decades, adolescent pregnancy has emerged as a significant healthcare issue in both developed and developing countries. However, it is not a new phenomenon. According to the World Health Organization, adolescent pregnancy refers to pregnancies in women aged 10 to 19 years, with those aged 10-15 often considered as a distinct group [1, 2]. Adolescence is a transitional period during which a carefree child becomes a responsible, reproductive individual [3]. This phase is marked by rapid physical, psychological, socio-cultural, and cognitive changes that adolescents must navigate in a short time while establishing their identity and autonomy [4]. The onset of adolescence begins with puberty, signified by the first menstruation (menarche) in females [5]. Recent decades have seen a trend towards earlier menarche, initiating the reproductive period earlier, the long-term consequences of which are still unclear.

In Serbia, 29% of adolescents aged 15-19 years have had sexual experiences. Young people often lack a well-developed awareness of the importance of safe and responsible sexual behavior, placing them at higher risk for negative outcomes from sexual activity. Early sexual encounters are risky, leading to unintended pregnancies and associated consequences: physical risks from abortion, as well as familial, economic, psychological, and social impacts. Additionally, there is an increased risk of sexually transmitted diseases and a tendency towards later promiscuity, which can hinder the formation of stable relationships and marriages. The likelihood of complications is higher in young adolescent women – preterm delivery, miscarriage, stillbirth, and maternal mortality are four times more likely compared to women over 20 years old [1]. Newborns of adolescent mothers more frequently have low birth weights due to prematurity and intrauterine growth retardation [6]. Adolescence, being a critical period for psychological development and identity formation, can lead to adolescent mothers experiencing a "syndrome of lost adolescence" – difficulty in forming a stable identity and achieving independence. Long-term consequences of adolescent pregnancy also include certain destructive behaviors such as smoking, drug use, alcoholism, and frequent changes in sexual partners [1, 7].

Material and Methods

The data for this study were retrieved from the archives of the Clinic for Gynecology and Obstetrics at the University Clinical Center of Vojvodina (OBGYN UCCV). The study encompassed all patients aged 10-19 years who delivered at the Clinic between January 1 and December 31, 2020. Medical records included information such as the patients' age, residence, occupation, body weight, height, external conjugate diameter measurement, number of pregnancies, parity, gestational age, mode of delivery, blood loss, length of hospital stay, and any pregnancy-related complications. Data on newborn birth weights and Apgar scores at the first and fifth minute were also collected.

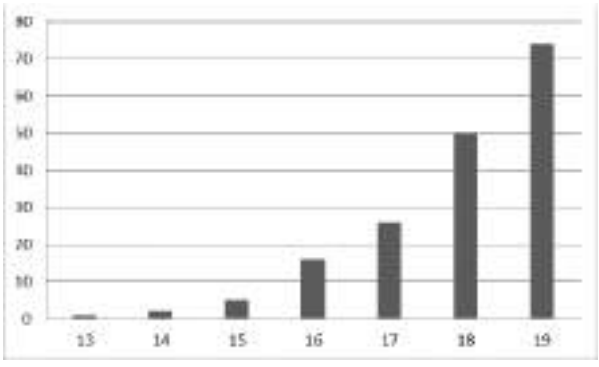
All collected data were analyzed using the IBM Statistical Package for the Social Sciences statistical software. Numerical variables were presented as mean, mode, and median values, along with measures of variability such as standard deviation. Categorical variables were presented as frequencies and percentages. The Student t-test was used to compare numerical variables between groups, while differences in categorical variables were assessed using the Chi square test (χ^2). Statistical significance was set at $p<0.05$.

Results

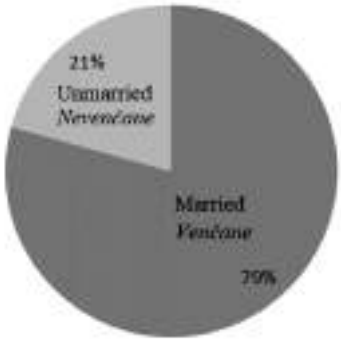
Out of a total of 6622 deliveries at the Clinic for Gynecology and Obstetrics of the University Clinical Center of Vojvodina in 2020, 174 were among adolescents (2.63%). **Graph 1** illustrates the distribution of patients by age. The average age of adolescents giving birth in 2020 was 17.93 ± 1.24 years (MIN 13, MAX 19). The youngest mother was 13 old, and the largest group (74/174) consisted of 19–year-olds. Adolescents aged 15 or younger constituted 4.59% (8/174) of the sample, while those aged 16-19 years made up 95.4% (166/174). Among all adolescent patients at OBGYN UCCV in 2020, 36/174 (20.69%) were married, and 138/174 (79.31%) were unmarried **(Graph 2).**

Based on collected body weight and height data, adolescents had an average body weight of 71.51 ± 14.74 kg (MIN 44, MAX 120) and an average height of 160.79 ± 10.73 cm (MIN 65, MAX 180). The average body mass index among adolescents who gave birth was 28.09 ± 10.26 kg/m^2 (MIN 16.36, MAX 142.01).

The average external pelvic measurements (conjugata externa) were 16.25 ± 1.16 cm (MIN 13,



Graph 1. Distribution of patients by age
Grafikon 1. *Starosna distribucija pacijentkinja*

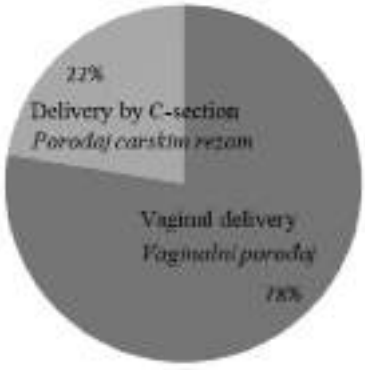


Graph 2. Marital status of patients
Grafikon 2. *Bračni status pacijentkinja*

MAX 20). There were no statistically significant differences in pelvic measurements between adolescents aged 15 or younger and those aged 16-19 years (p=0.14). Similarly, no significant differences were found in birth weight (p=0.3), birth length (p=0.28), blood loss (p=0.11), or length of hospital stay (p=0.35) between adolescents with conjugata externa ≤15 cm and >15 cm.

However, adolescents with conjugata externa of 15 cm or less had a statistically significantly longer hospital stay post-delivery (p=0.04). There were no statistically significant differences in the mode of delivery between these two groups (p=0.75). On average, adolescents stayed in the hospital for 5.94 ± 3.36 days (MIN 2, MAX 24, MODE 3), and the average time from delivery to discharge was 4.73± 2.47 days (MIN 2, MAX 20, MODE 3).

Among adolescents who gave birth at the OBGYN UCCV in the 2020, 135 out of 174 (77.59%) delivered vaginally, and 39 out of 174 (22.41%) via caesarean section **(Graph 3).** The hospital stay of adolescents who delivered via caesarean section was significantly longer compared to those who delivered vaginally (p=0.00000099). Hospitalization duration was statistically significantly longer for patients aged 15 years or younger compared to those aged 16-19 years (p=0.04). The time from delivery to discharge was also significantly longer for patients aged 15 years or younger (p=0.008). The values of external conjugate in adolescents did not show a statistically significant impact on the mode of delivery (p=0.27%). There were no statistically significant associations between the patients' age and mode of delivery (p=0.45), nor between the length of pregnancy and the mode of delivery (p=0.06).



Graph 3. Mode of delivery in adolescents
Grafikon 3. *Način porođaja adolescentkinja*

Newborns of adolescents who delivered via caesarean section had significantly lower birth weights (2993±613 g vs. 3212±500 g, p=0.01) and shorter body length (47±2.5 cm vs. 49 ±2.2 cm, p=0.001) than those delivered vaginally.

An analysis of the mode of delivery concerning the adolescents' educational level (elementary school/high school and college), place of residence (village/town), and marital status (unmarried/married) revealed no statistically significant differences (p=0.91, p=0.19, p=0.67 respectively).

Episiotomy was performed on 91 out of 135 (67.41%) patients, while it was not needed in the remaining 44 out of 135 (32.59%). On average, the adolescents experienced a blood loss of 451.69 ± 129.64 ml (MIN 300, MAX 1450). Two patients experienced a more significant blood loss of 1450 ml and 1300 ml, respectively. Both patients were 19 years old. One patient, aged 15, lost 860 ml of blood. Although the average blood loss during delivery for adolescents aged 15 or younger (532±190 ml) was higher than that for adolescents aged 16-19 (488±127 ml), the difference was not statistically significant (p=0.07). No significant differences in blood loss were found between the two groups of adolescents with regard to the external conjugate measure (≤15 cm vs. >15 cm) (p=0.11).

The average number of pregnancies in adolescents was 1.32 ± 0.6 (MIN 1, MAX 4), and the average parity was 1.21 ± 0.48 (MIN 1, MAX 4). The average gestational age at delivery did not differ significantly with respect to the adolescents' age (≤15 years 38.85±2.8 vs. 38.93±1.88, p=0.45). A total of 178 babies were born from 174 pregnancies, with four being twin pregnancies (2.3%). Of the newborns, 99 (55.62%) were male and 79 (44.38%) were female. The average birth weight of newborns was 3186.06 ± 509.24 grams (MIN 1160, MAX 4450), and the average birth length was 48.91 ± 2.27 cm (MIN 37, MAX 54). The parameters of birth weight and length for newborns born to mothers aged 13-15 were compared to mothers aged 16-19 years. No statistically significant differences were found in birth weight and length between these two groups of adolescents (p=00.19 and p=0.12 respectively).

Discussion

The number of adolescent deliveries is showing a slight downward trend both in our country and globally. We analyzed a period of twenty five years, drawing on studies conducted at the Clinic for Gynecology and Obstetrics of the University Clinical Center of Vojvodina. The frequency of adolescent births decreased from 7.54% in 1992 to 2.63% in 2020, with intermediate drops to 6.61% in 1996, 5.66% in 1999, 4.51% in 2002,2.22% in 2008, and 2.07% in 2012 [1, 8]. In the United States, the fre-

quency rate of adolescent births fell from 6.18% in 1991 to 3.13% in 2011 [9]. Similarly, in Great Britain, the rate of adolescent pregnancies was reduced almost by almost half from 1999 to 3.83% in 2009 [10].

Caesarean sections are becoming increasingly common worldwide, often without clear indications. At the OBGYN UCCV, the frequency of caesarean sections in the general patient population tippled from 9.7% in 1992 [1] to 21.87% in 2003 [8], 31.84% in 2012, reaching 33.69% in 2020. A similar trend is observed globally, with the USA where the frequency rate of delivery by caesarean section was 20.7% in 1996, only to record a constant rise over the next 15 years and to reach 32.8% in 2011 [9]. At our clinic, adolescents have significantly less C-sections than adult patients. It is presumed that young patients will have more pregnancies and births in their future life, which could influence the obstetrician's decision to avoid scarring the uterus. Despite adolescent pregnancies and births being considered high risk, the percentage of adolescent C-sections at our clinic was 22.41% in 2020. Data obtained in previous studies revealed that the percentage of adolescent deliveries by caesarean section at the OBGYN UCCV was 3.27% in 1992 [1], leading to a conclusion that the C-section rate in adolescents increased 7 times by 2020, an increase that is approximately twice the increase observed in the general patient population over the period of 30 years.

The rate of caesarean sections exceeds the World Health Organization's recommendation rate of 15% [11]. The frequent use of C-sections among adolescents might be attributed to pelvic immaturity, leading to cephalopelvic disproportion, particularly in those under 15 years of age. However, our study found no significant difference in pelvic development (measured by external conjugate) between adolescents aged 15 or younger and those aged 16-19. This suggests that the number of years since menarche may be a more critical factor for pelvic development than chronological age. Interestingly, adolescents aged 15 years or younger had a C-section rate of 37.5%, compared to 21.69% for older adolescents, and that newborns had lower birth weights and lengths. This raises the question of whether C-sections are justifiably more common in younger adolescents.

In the 2020, 77.59% of adolescent deliveries at the OBGYN UCCV were vaginal. This can be attributed to the better functioning of the young myometrium, a less competent cervix, and greater connective tissue elasticity in young women. The percentage of episiotomies among adolescents has fluctuated over the years, with a high of 68.84% in 1992, dropping to 55.35% in 2002 [1], and 45.86% in 2012, and rising again to 67.41% in 2020. This high percentage can be explained by the fact that most adolescents were first time mothers.

Our study found no statistically significant impact of place of residence, educational level, or marital status on the delivery outcomes of adolescents.

However, the physical immaturity and frequent anemia in adolescent pregnancies and puerperium make blood loss during delivery a significant factor. While the common blood loss in vaginal delivery is approximately 500 ml and up to 1000 ml in C-section [12], our study found a higher average blood loss in younger adolescents, though the difference was not statistically significant.

Studies often describe babies born to adolescent mothers as having low birth weights due to prematurity and intrauterine growth retardation [13, 14], placing them at high risk of perinatal morbidity and mortality. Our study found no statistically significant relationship between the adolescents' age and their newborns' birth weight and length, likely due to small sample size and the good prenatal care provided.

However, our study did find that newborns of adolescents who delivered by C-section had significantly lower birth weights and lengths compared to those delivered vaginally.

The length of hospitalization and the time from delivery to discharge are critical factors in the recovery of adolescents, both physically and psychologically. Our study showed that these durations were significantly longer for those who delivered by C-section, where younger than 15 years, or had external pelvic measurements are 15 cm or less. Prolonged hospital stays are often due to delivery complications and to the need for extended medical care for the mother or child.

Adolescent behaviors have changed over the years, with younger initiation of sexual activity and varying contraceptive use. The decrease in adolescent births may result from increased contraception use or more abortions. Earlier studies at the OBGYN UCCV indicate that contraceptive use has not significantly increased, adolescents are more likely to opt not to give birth [1], impacting their later psychosocial circumstances.

Providing adequate healthcare, timely information, and social and economic support can reduce unintended pregnancies in adolescence, preventing significant late consequences.

Conclusion

The frequency of adolescent births has decreased threefold over the last 25 years. Although the rate of caesarean sections among adolescents has increased, it remains significantly lower than in the general population. Pelvic size is likely associated not only with age but also with the time since puberty and other factors not included in this study. Newborns of adolescents who delivered by C-section have lower birth weights and lengths. Adolescents who gave birth by C-section, those younger than 15 years, and those with external pelvic measurements of 15 cm or less require longer hospital stays. While adolescent pregnancies and births are declining, they still pose significant risks. Therefore, enhancing prenatal and perinatal care, promoting the social and economic status of the population, and improving adolescent reproductive health education and healthcare can further reduce the rate of teen pregnancies and ensure healthy pregnancy and delivery outcomes for adolescents.

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HYPOTHESIS TESTING AND STATISTICAL TEST SELECTION: FUNDAMENTALS OF STATISTICS IN CLINICAL STUDIES – PART II

TESTIRANJE HIPOTEZE I IZBOR STATISTIČKOG TESTA: OSNOVE STATISTIKE U KLINIČKIM ISTRAŽIVANJIMA – DEO II

Božana NIKOLIĆ[1,2] and Tamara POPOVIĆ[3]

Summary
Hypothesis testing is a systematic procedure for evaluating assumption about difference or relationship between variables. This process involves four main steps: formulating a hypothesis, establishing decision-making criteria, calculating statistical values, and drawing a conclusion. In clinical studies, the process begins with the formulation of a hypothesis, which includes both the alternative and null hypothesis. Statistical tests are employed to assess the null hypothesis by calculating key statistical values, such as the test statistic and p-value. Based on the p-value, conclusions are made regarding the presence of a significant difference or relationship between the variables under study. The selection of an appropriate statistical test depends on various factors, and understanding these factors is crucial for making valid inferences and accurately interpreting clinical study results. This professional article outlines the steps involved in hypothesis testing and discusses the key considerations for selecting the appropriate statistical test.
Key words: Research Design; Models, Statistical; Statistics as Topic; Data Interpretation, Statistical

Sažetak
Testiranje hipoteze je sistematski postupak u kome se proverava pretpostavka o razlici ili vezi između varijabli. Može se razložiti u četiri koraka: postavljanje hipoteze, određivanje kriterijuma za donošenje odluke, izračunavanje statističkih veličina, te donošenje odluke odnosno zaključka. Klinička istraživanja započinju postavljanjem hipoteze, koja ima dva oblika: alternativni i nulti. Statistički testovi proveravaju nultu hipotezu i izračunavaju statističke veličine (statistiku testa i p-vrednost). Na osnovu p-vrednosti se donosi zaključak o postojanju razlike ili veze između varijabli. Izbor statističkog testa zavisi od nekoliko faktora a njihovo poznavanje je neophodno za donošenje validnih zaključaka i ispravno tumačenje rezultata kliničkog istraživanja. Ovaj stručni rad opisuje korake u testiranju hipoteze i faktore koji su od značaja za izbor odgovarajućeg statističkog testa.
Ključne reči: dizajn istraživanja; statistički modeli; statistika kao tema; statistička interpretacija podataka

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Introduction

Clinical studies enhance our understanding of the etiology, diagnosis, prevention, prognosis, treatment, and outcome of diseases. These studies are conducted under specific conditions defined by the study design, inclusion and exclusion criteria, variables to be measured, and other parameters. However, these conditions do not perfectly reflect real-life scenarios, as real-life conditions cannot be precisely defined [1]. Despite this, clinical studies aim to simulate real-life as closely as possible, making it crucial to select a sample that is representative of the target population (e.g., children, women, patients with diabetes). In practice, the entire population is rarely accessible, and even in smaller populations, it is nearly impossible to recruit all individuals within it [1, 2].

After sampling, subjects are classified into groups and monitored by measuring various variables. The results of these measurements are then generalized to the entire population based on the inferences drawn through hypothesis testing [2].

Statistical inference, or hypothesis testing, involves four main steps: formulating a hypothesis, establishing decision-making criteria, calculating statistical values from the sample data, and drawing a conclusion or inference [3]. For instance, in a ran-

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Abbreviations
COVID-19 – Corona Virus Disease of 2019
H_0 – null hypothesis
ND – normal distribution
RM – repeated measurements
ANOVA – analysis of variance

domized controlled trial, it was hypothesized that preoperatively administered liraglutide would reduce the number of cardiac surgery patients requiring intraoperative insulin for glycemic control [4]. A decision-making criterion was established (α=0.05), what will be discussed later. The chi-square test was used to evaluate the hypothesis and compute statistical values (χ^2 and p-value). Based on the p-value, a conclusion was made regarding the acceptance of the hypothesis [4].

This professional article outlines the steps involved in hypothesis testing and discusses the key factors relevant for selecting the appropriate statistical test.

Null Hypothesis, Type I error, Type II error, and Test Power

Clinical studies, particularly randomized controlled trials, begin with the formulation of one or more hypotheses to be tested [1]. A hypothesis is an assumption regarding a difference or relationship between two or more variables, and it can take two forms: the alternative hypothesis and the null hypothesis. The alternative hypothesis posts that there is a significant difference between the variables. In contrast, the null hypothesis assumes the opposite: there is no significant difference between the variables, and any observed difference is due to chance [1, 3].

Although the focus is on the alternative hypothesis, statistical testing is conducted on the null hypothesis. The process begins with the assumption that the null hypothesis is true, and efforts are made to gather evidence to reject it. The alternative hypothesis is not directly tested; it is automatically accepted as true if there is sufficient evidence to reject the null hypothesis [2, 3].

When testing a null hypothesis, there are four possible outcomes: two correct and two incorrect [1, 3]. An inference is correct if the true null hypothesis is accepted or if the false null hypothesis is rejected. Conversely, an inference is incorrect if the true null hypothesis is rejected (Type I error) or if the false null hypothesis is accepted (Type II error). A Type I error is a false positive, where it is incorrectly inferred that there is a difference between two variables when there is actually no difference. The probability of committing a Type I error is denoted by the significance level α. A Type II error is a false negative, where it is incorrectly concluded that there is no difference between two variables when a difference does exist. The probability of committing a Type II error is denoted by β [1, 3, 5, 6] **(Table 1)**.

The power of a test is related to the Type II error and it is calculated 1-β. By definition, it is the probability that the test will detect a difference or relationship in the sample when such a difference or relationship actually exists in the population [1, 3, 5, 6]. Tests with low power may fail to identify a statistically significant difference or relationship; conversely, excessively high test power may lead researchers to overstate the significance of a statistical difference or relationship beyond what is justified by clinical practice [6].

There is a trade-off between Type I and Type II errors: reducing α increases β, and vice versa. Ideally, both α and β should be 0%, but this is unattainable due to sampling variability, which is an inherent part of any clinical study. Consequently, by convention, α is typically set at 5%, and β at 20% or 10% [1]. This implies that 5% probability of a false positive and a 20% or 10% probability of a false negative are deemed acceptable. Accordingly, the acceptable power of a test is 80% or 90%.

P-value

A statistical test computes a test statistic and the associated p-value. Based on the p-value, an inference is made about whether to accept or reject the null hypothesis [1, 3, 5, 6]. The p-value, representing the computed level of statistical significance, is compared with the predetermined level of statistical significance (α). If the p-value is less than α, the null hypothesis is rejected; conversely, if the p-value is equal to or greater than α, the null hypothesis is accepted. For example, α is conventionally set to 0.05. This means that if the p-value is less than 0.05, the null hypothesis is rejected because it is unlikely that the observed difference between the variables is due to chance. Conversely, if the p-value is equal to or greater than 0.05, the null hypothesis is accepted because it is highly likely that the observed difference between the variables is due to chance [1, 3, 5, 6]. Therefore, the p-value is conceptually related to α, it is not the same as α.

Choosing a statistical test

There are numerous statistical tests, and those commonly used are listed in **Tables 2 and 3** [7–10].

Table 1. Four inferences in the null hypothesis testing
Tabela 1. *Četiri zaključka kod testiranja nulte hipoteze*

	True H_0/*Tačna* H_0	False H_0/*Netačna* H_0
Fail to reject H_0/H_0 *se ne odbacuje*	Correct inference/*Ispravan zaključak*	Type II error/*Greška tipa II*
Reject H_0/H_0 *se odbacuje*	Type I error/*Greška tipa I*	Correct inference/*Ispravan zaključak*

Legend: H_0 – null hypothesis/*Legenda*: H_0 – *nulta hipoteza*

Table 2. Statistical tests employed to test the difference between variables [6, 7, 10, 13].
Tabela 2*. Statistički testovi koji se koriste za ispitivanje razlike između varijabli [6, 7, 10, 13].*

Dependent variable *Zavisna varijabla*			Independent variables *Nezavisne varijable*			
Scale of measurement *Skala merenja*	ND *NR*	RM *PM*	Measurements (N) *Merenja* (N)	Number *Broj*	Groups (N)* *Grupe* (N)*	Statistical test *Statistički test*
Quantitative *Kvantitativna*	Yes *Da*	No *Ne*	1	1	2	Unpaired Student′s t-test *Neupareni Studentov t-test*
Ordinal, quantitative *Ordinalna, kvantitativna*	No *Ne*	No *Ne*	1	1	2	Mann-Whitney U-test *Man-Vitnijev U-test*
Quantitative *Kvantitativna*	Yes *Da*	No *Ne*	1	1	≥3	One-way ANOVA *Jednofaktorska ANOVA*
Ordinal, quantitative *Ordinalna, kvantitativna*	No *Ne*	No *Ne*	1	1	≥3	Kruskal-Wallis test *Kruskal-Volisov test*
Qualitative *Kvalitativna*	–	No *Ne*	1	1	≥2	Chi-square test *Hi-kvadrat test*
Quantitative *Kvantitativna*	Yes *Da*	Yes *Da*	2	1	2	Paired Student′s t-test *Upareni Studentov t-test*
Ordinal, quantitative *Ordinalna, kvantitativna*	No *Ne*	Yes *Da*	2	1	2	Wilcoxon′s rank test *Vilkoksonov test ranga*
Quantitative *Kvantitativna*	Yes *Da*	Yes *Da*	≥3	1	≥3	Paired one-way ANOVA *Uparena jednofaktorska ANOVA*
Ordinal, quantitative *Ordinalna, kvantitativna*	No *Ne*	Yes *Da*	≥3	1	≥3	Friedman′s test *Fridmanov test*
Dichotomous *Dihotomna*	–	Yes *Da*	2	1	2	McNemar′s test *Maknemarov test*
Dichotomous *Dihotomna*	–	Yes *Da*	≥3	1	≥3	Cochran′s Q test *Kohrejnov Q test*

*Two and three groups in statistical tests with repeated measurements are time 1/time 2 and time 1/time 2/time 3, consequently.
**Dve i tri grupe u statističkim testovima sa ponovljenim merenjima su vreme 1/vreme 2 i vreme 1/vreme 2/vreme 3, redom.*
Legend: ND – normal distribution; RM – repeated measurements; ANOVA – analysis of variance
Legenda: NR – normalna raspodela; *PM – ponovljena merenja*; *ANOVA – analiza varijans*e

The choice of an appropriate test depends on several factors, including the study hypothesis, the scale of measurement for the dependent variable, the distribution shape of the dependent variable, the number of measurements of the dependent variable, and the number of independent variables along with their scales of measurement [6, 10].

Study hypothesis

The first factor to consider when choosing a statistical test is the study hypothesis, which can involve an assumption about a difference or a relationship between two or more variables. When testing a hypothesis about a difference (e.g., therapy outcomes differing between two groups of patients), the guidelines given in **Table 2** should be followed. Conversely, when testing a hypothesis about a relationship (e.g., a relationship between patient age and cardiovascular events), the guidelines given in **Table 3** should be followed.

Scale of measurement for the dependent variable

Another crucial factor to consider in selecting a statistical test is the scale of measurement for the dependent variable. This requires an understanding of nominal, ordinal, interval and ratio scales. Generally, nominal and ordinal scales are classified as qualitative, while interval and ratio scales are classified as quantitative [3]. Variables measured on a quantitative scale can be categorized, though this is not always ideal due to the potential loss of information. For instance, when assessing the effect of age on the risk of a cardiovascular event, younger individuals typically have a lower risk than older individuals. A researcher may decide to categorize the age into groups such as <18 years, 18-44 years, 45-64 years, and ≥65 years. However, this categorization results in a loss of detailed information, as the exact age of each subject becomes obscured. For example, a 44-year-old is considered the same as an 18–year-old since they fall into the same category, but they are treated differently from a 45-year-old who falls into a different category.

Distribution shape for the dependent variable

Statistical tests can be categorized as parametric and nonparametric [5, 7]. The choice between these depends on the distribution shape of the quantitative dependent variable. Parametric tests, such as Student′s t-test, analysis of variance (ANOVA), and Pearson′s correlation, are used when the distribution is normal **(Tables 2 and 3).** When there is a significant deviation from normal distribution, or when

Table 3. Statistical tests employed to test the relationship between variables [6, 7, 10, 13]
Tabela 3. *Statistički testovi koji se koriste za ispitivanje veze između varijabli [6, 7, 10, 13]*

	Dependent variable *Zavisna varijabla*			Independent variables *Nezavisne varijable*	
	Scale of measurement *Skala merenja*	ND *NR*	Number *Broj*	Scale of measurement *Skala merenja*	Statistical test *Statistički test*
Correlation *Korelacija*	Qualitative *Kvalitativna*	–	1	Qualitative *Kvalitativna*	Chi-square test or Fisher′s exact test *Hi-kvadrat test ili Fišerov test*
	Quantitative *Kvantitativna*	Yes *Da*	1	Quantitative *Kvantitativna*	Pearson′s correlation *Pirsonova korelacija*
	Ordinal, quantitative *Ordinalna, kvantitativna*	No *Ne*	1	Ordinal, quantitative *Ordinalna, kvantitativna*	Spearman′s correlation *Spirmanova korelacija*
Regression *Regresija*	Quantitative *Kvantitativna*	Yes *Da*	1	Quantitative or qualitative *Kvantitativna ili kvalitativna*	One-way linear regression *Jednostavna linearna regresija*
	Quantitative *Kvantitativna*	Yes *Da*	≥2	Quantitative or qualitative *Kvantitativna ili kvalitativna*	Multivariable linear regression *Višestruka linearna regresija*
	Dichotomous *Dihotomna*	–	1	Quantitative or qualitative *Kvantitativna ili kvalitativna*	Simple logistic regression *Jednostavna logistička regresija*
	Dichotomous *Dihotomna*	–	≥2	Quantitative or qualitative *Kvantitativna ili kvalitativna*	Multivariable logistic regression *Višestruka logistička regresija*
Agreement *Slaganje*	Qualitative/*Kvalitativna*	–	0	–	Cohen kappa/*Koenova kapa*
	Quantitative *Kvantitativna*	Yes *Da*	0	–	Intraclass correlation coefficient *Intraklasni koeficijent korelacije*

Legend: ND – normal distribution/*Legenda*: *NR – normalna raspodela*

the dependent variable is measured on an ordinal or nominal scale, nonparametric tests, such as Mann-Whitney U-test, Kruskal-Wallis test, Friedman′s test, and Spearman′s correlation, are employed **(Tables 2 and 3).** Generally, parametric tests have greater power than nonparametric tests to detect differences if they exist.

Testing the normality of distribution can be done using visual methods (distribution curve, Q-Q plot), measures that describe distribution shape (skewness and kurtosis), and statistical significance tests (e.g., Kolmogorov-Smirnov test, Shapiro-Wilk test) [11]. A normal distribution curve is symmetrical, bell-shaped, and has the mean, median, and mode nearly identical. A Q-Q plot indicates normal distribution if the data points lie along a diagonal line. Numerically, a distribution is considered normal if skewness and kurtosis values are zero, although values ranging between -2 and +2 are also acceptable [12]. The Kolmogorov-Smirnov test is commonly used to test normality, indicating a normal distribution if the computed p-value is above 0.05 [13].

Apart from normal distribution, variables can have a positively skewed distribution (most values are low) or a negatively skewed distribution (most values are high). Since parametric tests require normally distributed variables, the question arises about how to handle variables with asymmetric distribution. One option is to use nonparametric tests as an alternative to parametric tests [10, 13]. Another option is to transform variables that do not follow a normal distribution [10, 13]. Depending on the original distribution shape (positive or negative skewness), various mathematical transformations (e.g., square root, logarithm, inversion) can be applied to approximate normality [13]. For negatively skewed distribution, the data is first reflected to produce a positively skewed distribution before applying the appropriate transformation. There is a considerable debate in the literature regarding the transformation of variables; some researchers support it, while others against it due to the challenging interpretation of transformed variables and availability of nonparametric counterparts to most parametric tests, which do not rely on distribution assumptions.

Number of measurements of the dependent variable

A dependent variable can be measured once, twice or multiple times. When measurements are repeated, the values of one variable may influence the values of another, resulting in paired dependent variables [10]. For instance, Hemmati et al. examined the impact of physical activity on the immune system of patients after kidney transplantation [14]. The immune condition was assessed based on the cytokine profile, determined before the study and at week 12, upon completion.

Dependent variables are also considered paired when subjects are included in the study as pairs based on age, sex, clinical characteristics, or similar factors, with each subject in a pair exposed to different intervention [13]. For example, Feldman et al. compared the effects of different inhaled medications on clinical outcomes, measured by hospitalization rates and exacerbations in chronic obstructive pulmonary disease [15]. A matched cohort study included 30,216 pairs of subjects, where one subject in each pair used a long-acting muscarinic agonist/

long-acting beta-adrenergic agonist combination, and the other used an inhaled corticosteroid/long-acting beta-adrenergic agonist combination.

The number of measurements of the dependent variable is crucial when choosing the appropriate version of a statistical test. For example, the Student′s t-test has different versions or mathematical approaches depending on whether the dependent variable is measured once (unpaired Student′s t-test) or twice (paired Student′s t-test) **(Table 2)** [10]. The paired Student′s t-test was used in the study by Hemmati et al. [14].

Number of independent variables and their scale of measurement

When selecting a statistical test, it is essential to consider the number of independent variables, their scale of measurement, the number of groups (categories) of the independent variable, and whether there is an interaction between the independent variables [10]. Notably, the distribution shape of the independent variable is never a consideration in statistical analyses [10].

The number of independent variables is crucial when choosing a test for regression analysis **(Table 2).** For example, Awan et al. examined the relationship between spasticity and constipation in children with cerebral palsy [16]. Since spasticity was the sole independent variable, its relationship with constipation was tested using simple linear regression. In contrast, Qiao et al. included several independent variables, such as metabolic parameters (e.g., free fatty acids, triglycerides, total cholesterol, glucose, insulin), and tested their relationship with weight gain using multiple linear regression [17].

As for the scale of measurement, analysis of variance and regression analysis are mathematically equivalent [10]. However, analysis of variance is used when the independent variables are qualitative, whereas regression analysis can handle both qualitative and quantitative independent variables **(Tables 2 and 3).**

Study design can include one, two, three, or more groups. With only one group, comparisons are not possible, so descriptive statistical methods are used instead [2, 10]. For example, Montenegro et al. conducted a cross-sectional study among primary care patients with post COVID-19 to describe symptoms and prevalence using descriptive statistics such as mean and standard deviation for quantitative data (e.g., duration of symptoms) and percentage for qualitative data (e.g., prevalence of symptoms) [18]. In studies with two groups, an appropriate statistical test for comparison is required. For instance, Pajić et al. studied the characteristics of seizures in childhood acute gastroenteritis, dividing patients into febrile and afebrile group and comparing their characteristics (e.g., age) using the Student′s t-test, which compares means between two groups [19]. For studies with more than two groups, the statistical analysis becomes more complex. All groups are compared simultaneously using the appropriate test, and if a statistically significant difference is found, post hoc tests determine the significance of the differences between specific pairs of groups. For example, Akinbade et al. compared the effectiveness of analgesics on pain after surgical tooth extraction by randomizing patients into three groups (ibuprofen, celecoxib, and tramadol) and comparing the mean pain intensity scores using one-way ANOVA [20]. Since the test indicated a statistically significant difference ($p = 0.0039$), the post hoc tests were used to identify which pairs of groups differed significantly.

An interaction occurs when one independent variable affects another. In multiple linear regression, high correlation between independent variables (correlation coefficient ≥ 0.9) negatively impacts test quality. Therefore, it is advisable to exclude one of the highly correlated variables from the analysis or to combine them into a single independent variable [13].

Conclusion

Hypothesis testing involves four key steps: formulating a hypothesis, establishing decision-making criteria, calculating statistical values (test statistic and p-value) from the sample data, and drawing a conclusion or inference. The choice of an appropriate statistical test depends on several factors, including the study hypothesis, scale of measurement for the dependent variable, distribution shape, number of measurements of the dependent variable, number of independent variables, and their scales of measurement. A thorough understanding of these factors is essential for drawing valid inferences and correctly interpreting the results of clinical studies.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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LINGUAL THYROID IN A YOUNG ASYMPTOMATIC FEMALE PATIENT WITH HYPOTHYROIDISM – CASE REPORT

LINGVALNA ŠTITASTA ŽLEZDA KOD MLADE PACIJENTKINJE BEZ SIMPTOMA SA HIPOTIREOIDIZMOM – PRIKAZ SLUČAJA

Ivana STARČEVIĆ[1,2], Dolores SRBOVAN[1], Emil MATOVINA[1] and Jasna MIHAILOVIĆ[1,2]

Summary

Introduction. Lingual thyroid is a rare condition where thyroid tissue is abnormally located at the base of the tongue due to embryological development issues. The precise prevalence is uncertain, as many asymptomatic individuals do not undergo clinical examination. **Case report.** We present a case of a 28-year-old woman with a history of hypothyroidism. The patient exhibited no symptoms indicative of lingual thyroid. A neck ultrasound identified hypoplastic thyroid tissue centrally in the neck and a solitary nodule in the submandibular region. Further evaluation with an oropharyngeal examination revealed a solid mass at the base of the tongue. A technetium-99m pertechnetate thyroid scintigraphy, performed with single photon emission computed tomography on a hybrid gamma camera, demonstrated functional thyroid tissue at the tongue's base, measuring 16 mm in diameter, with no functional glandular tissue in the central neck region. **Conclusion.** Asymptomatic lingual thyroid can be diagnosed through oropharyngeal examination, neck ultrasound and technetium-99m pertechnetate thyroid scintigraphy using a hybrid gamma camera, which provides both functional and anatomical data. Management should be individualized based on the patient's symptoms and thyroid hormone levels.

Key words: Lingual Thyroid; Hypothyroidism; Thyroid Dysgenesis; Diagnosis; Ultrasonography; Radionuclide Imaging

Sažetak

Uvod. Lingvalna štitasta žlezda je retka ektopična lokalizacija štitaste žlezde koja se javlja u vidu čvora na bazi jezika zbog abnormalnosti u embriogenezi. Tačna učestalost lingvalne štitaste žlezde nije poznata jer mnogi asimptomatski pojedinci nikada ne dođu na klinički pregled. **Prikaz slučaja.** Prikazan je slučaj pacijentkinje stare 28 godina koja se javila na naše odeljenje sa kliničkom istorijom hipotireoze. Pacijentkinja nije prijavila nikakve simptome koji bi ukazivali na prisustvo lingvalne štitaste žlezde. Ultrasonografskim pregledom vrata otkriveno je hipoplastično tkivo štitaste žlezde u centralnom delu vrata i solitarni čvor u submandibularnoj regiji. Radi dodatne evaluacije urađen je orofaringealni pregled kojim je uočena solidna masa na bazi jezika. U našoj službi izvršena je studija scintigrafije štitaste žlezde tehnecijumom-99m pertehnetatom uz upotrebu jednofotonske emisione kompjuterizovane tomografije na hibridnoj gama kameri. Slike su pokazale funkcionalno tkivo štitaste žlezde u predelu baze jezika sa većim prečnikom od 16 mm i odsustvo funkcionalnog žlezdanog tkiva u centralnoj regiji vrata. **Zaključak.** Prisustvo lingvalne štitaste žlezde kod pacijenata bez simptoma može se dijagnostikovati putem orofaringealnog pregleda, ultrazvučnog pregleda vrata i scintigrafije štitaste žlezde tehnecijumom-99m pertehnetatom uz upotrebu hibridne gama kamere koja istovremeno pruža funkcionalne i anatomske informacije. Lečenje pacijenata sa lingvalnom štitastom žlezdom treba da bude personalizovano i zasnovano na simptomima pacijenta i statusu tiroidnih hormona.

Ključne reči: lingvalna štitasta žlezda; hipotireoidizam; ektopična štitna žlezda; dijagnoza; ultrasonografija; radionuklidni imidžing

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Introduction

Lingual thyroid (LT) is a rare condition characterized by the presence of thyroid tissue at the base of the tongue, resulting from its incomplete migration from the foramen caecum to the pretracheal region during embryogenesis [1]. The occurrence rate of LT ranges from approximately 1 in 100,000 to 300,000 individu-

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Abbreviations

LT	– lingual thyroid
CT	– computed tomography
MRI	– magnetic resonance imaging
FNAC	– fine-needle aspiration cytology
FT4	– free thyroxine
TSH	– thyroid-stimulating hormone
SPECT/CT	– single photon emission computed tomography/ computed tomography
EET	– ectopic thyroid tissue

als, with a higher prevalence among females [2, 3]. Despite these estimates, the exact frequency of LT remains uncertain due to the large number of asymptomatic individuals who do not seek clinical evaluation.

Although most patients with LT are asymptomatic, symptoms can arise from the enlargement of the glandular tissue. Common symptoms include a sensation of a lump in the throat, dysphagia, dysphonia, coughing and loud snoring [1, 4]. Approximately one-third of individuals with ectopic thyroid tissue exhibit clinical manifestations of hypothyroidism due to its typically inadequate production of thyroid hormones by the ectopic tissue [1, 5]. In about 70% of cases, LT is the only functioning thyroid tissue [6], and the simultaneous presence of LT and a normally positioned thyroid gland is extremely rare [7, 8]. The diagnosis of LT typically involves a combination of clinical assessment and various diagnostic procedures, including biochemical tests, neck ultrasonography, thyroid scintigraphy, computed tomography (CT) scans, and magnetic resonance imaging (MRI).

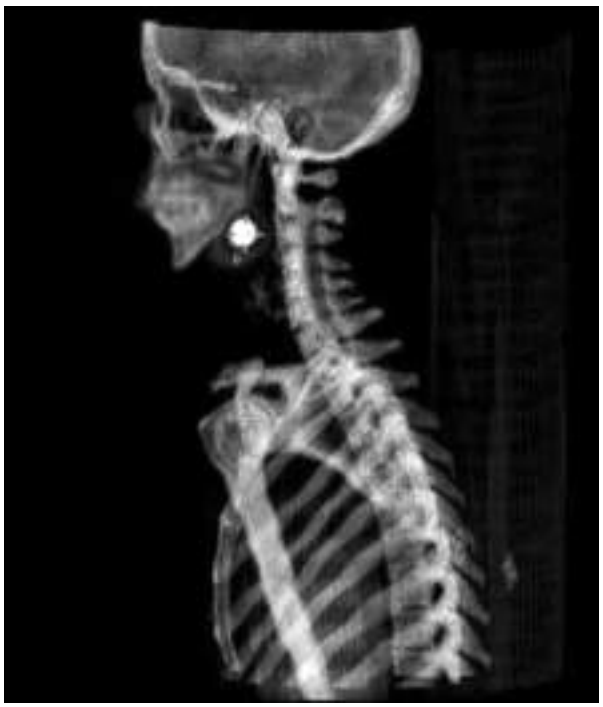

Figure 1. SPECT scan image, lateral view showing intense technetium-99m uptake in the tongue base area
Slika 1. *SPECT sken slike, lateralni snimak – prikazuje intenzivno nakupljanje tehnecijuma-99m u predelu baze jezika*

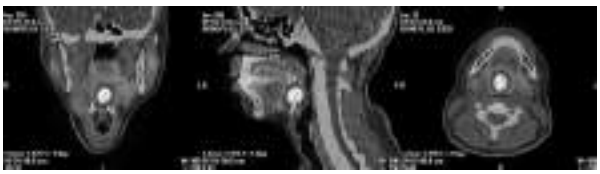

Figure 2. SPECT/CT fusion images showing intense technetium-99m uptake in the tongue base area
Slika 2. *SPECT/CT fuzione slike pokazuju prikazuje intenzivno nakupljanje tehnecijuma-99m u predelu baze jezika*

Fine-needle aspiration cytology (FNAC) also plays crucial role in confirming the diagnosis [1, 9, 10].

In this case report, we present a rare instance of a young female patient with hypothyroidism who exhibited non-functional thyroid tissue in its typical cervical location alongside functional ectopic LT tissue, despite being asymptomatic.

Case report

We present a case of a 28-year-old female who was referred to our department for further evaluation due to clinical concerns suggesting a possible presence of a lingual thyroid (LT).

Suspicion of LT arose from initial ultrasound findings and an oropharyngeal examination. A neck ultrasound revealed hypoplastic thyroid tissue in the central cervical region and a solitary isoechoic nodule in the submandibular area. Additional evaluation with an oropharyngeal examination revealed a solid mass at the base of the tongue. There was no enlargement of the cervical lymph nodes, and other physical examination findings were unremarkable. The patient's medical history indicated a diagnosis of hypothyroidism at the age of 12, with consistent adherence to levothyroxine replacement therapy since that time. The daily dosage of levothyroxine has consistently been 25 mcg. At the most recent check-up, laboratory tests showed a free thyroxine (FT4) level of 13.04 pg/dL (normal range, 9-19 pg/dL), and a thyroid-stimulating hormone (TSH) level of 1.05 IU/mL (normal range, 0.35-4.94 IU/mL). The patient did not report any symptoms indicative of LT.

In our department, we performed a single photon emission computed tomography/computed tomography (SPECT/CT) scan with technetium-99m pertechnetate. The SPECT and SPECT/CT fusion images revealed functional thyroid tissue at the base of the tongue with a diameter of 16 mm, and no functional glandular tissue in the central cervical position **(Figures 1 and 2)**. This confirmed the diagnosis of LT ectopia. Given the absence of symptoms, we recommended regular follow-up for the patient, including periodic assessment of hormonal levels and ultrasound examinations of the neck.

Discussion

The thyroid gland begins its development around the 24th day of gestation, making it the earliest en-

docrine gland to form in the human body. Occasionally, during embryonic development, the thyroid gland fails to properly migrate from its initial position at the base of the tongue to its final pre-tracheal location in the neck. This anomaly results in the presence of functional thyroid tissue in an atypical location, known as ectopic thyroid tissue (ETT) [2, 11, 12]. EET can be found along the thyroid's descent path, either in the midline or laterally within the neck. It may also occur in more distant regions, such as the mediastinum, beneath the diaphragm, or in various other locations throughout the body [2]. Approximately 90% of the reported ETT cases are found at the base of the tongue [13]. The first documented case of ectopic thyroid in a newborn reported by Hickman in 1869 [7]. The exact factors contributing to the failure of descent in cases of LT are still unclear. However, some researchers suggest a potential link between maternal antithyroid immunoglobulins and impaired gland descent during early fetal development [5]. Additionally, molecular irregularities, including mutations in genes crucial for thyroid development and differentiation, may also play a role in these migration anomalies, although more extensive investigations are necessary. For instance, the expression levels of certain genes vary depending on the anatomical location of the thyroid tissue [14].

Diagnosing LT presents a clinical challenge due to its often asymptomatic nature and atypical presentation [1]. In our case, the diagnosis of LT ectopia was confirmed through a combination of clinical examination and diagnostic imaging, consistent with previous reports [1, 5, 6]. Approximately 33% of patients with LT are hypothyroid and without remarkable clinical manifestations [5], as was the case with our patient. Inadequate blood supply to the ectopic thyroid gland, necessary for normal function, along with iodine organification defects, are potential causes of hypothyroidism [15]. The absence of symptoms in our patient can be attributed to adequate substitution therapy, which generally maintains the thyroid gland's volume [16]. In 93% to 100% of LT cases, the orthotopic thyroid tissue is absent [17]. However, this was not observed in our patient, as the neck ultrasound revealed the presence of a hypoplastic thyroid gland in its typical pre-tracheal location. Despite the presence of thyroid tissue in its orthotopic location, SPECT/CT images revealed its dysfunctionality, with the LT tissue at the base of the tongue being the only functional thyroid tissue. These findings are consistent with previous research, indicating that if LT tissue is present, it is often the only functional thyroid tissue in the body [1, 3, 6]. In our case, FNAC confirmation was not required, but the potential importance of FNAC should be considered, especially if suspicious focal changes in the LT tissue are present, as cases of thyroid carcinoma originating from ETT have been reported [6, 18]. Certain ultrasound features in thyroid nodules, such as marked hypoechogenicity, irregular margins, microcalcifications, and a taller-than-wide shape, are commonly associated with a higher risk of malignancy. Consequently, clinicians should consider performing FNAC in these cases [19].

The management of LT depends on several factors, including the presence of symptoms, the size and location of the ETT, and the patient's thyroid function status. In asymptomatic cases with preserved thyroid function, regular monitoring of function and morphology may be appropriate. In patients with hypothyroidism, hormone replacement therapy and follow-up is considered sufficient if there are no other symptoms, as was the case with our patient. However, symptomatic patients may require intervention, which may include surgical excision or radioiodine therapy [1, 11, 20]. Radioiodine ablation is recommended for those presenting with high-risk symptoms. In cases where symptoms are resistant to conservative therapy, malignancy is suspected, or high-risk symptoms preclude the use of radioiodine, surgical intervention should be considered [20, 21].

Conclusion

Lingual thyroid in asymptomatic patients can be effectively diagnosed through oropharyngeal examination, neck ultrasound, and technetium-99m pertechnetate thyroid scintigraphy using a hybrid gamma camera that provides both functional and anatomical information. The management of patients with lingual thyroid should be personalized, taking into account the patient's symptoms and thyroid hormone status.

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URINOMA MIMICKING PANCREATIC PSEUDOCYST – CASE REPORT

URINOM ILI PSEUDOCISTA PANKREASA − PRIKAZ SLUČAJA

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Summary

Introduction. A urinoma is a localized urine collection in the retroperitoneum, occurring outside the urinary tract. Although relatively rare, traumatic urinomas in pediatric patients pose significant diagnostic and therapeutic challenges. Initial diagnosis primarily relies on ultrasonography, but computed tomography (CT) and magnetic resonance imaging (MRI) provide clearer differentiation and localization. The treatment strategy focuses on preventing potential complications and promoting urinary tract recovery. **Case Report.** We present the case of a seventeen-year-old male with a penetrating abdominal injury. Prompt abdominal exploration revealed and managed minor colon and spleen lacerations. Upon readmission due to the fever and abdominal pain, further diagnostics initially misinterpreted the formed traumatic urinoma as a pancreatic pseudocyst. Postoperative computed tomography, cystoscopy, and retrograde pyelography subsequently confirmed the existence of a urinoma. **Conclusion**. Through this case report and its atypical manifestation, we aim to highlight the importance of differential diagnosis, the complexity of abdominal injuries, and diagnostic and treatment protocols in pediatric populations. Emphasizing a multidisciplinary strategy is crucial to optimizing treatment outcomes.

Key words: Pancreatic Pseudocyst; Urinoma; Diagnosis, Differential; Abdominal Injuries; Wounds, Penetrating; Ureter; Treatment Outcome; Adolescent; Tomography, X-Ray Computed; Nephrostomy, Percutaneous

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Sažetak

Uvod. Urinom predstavlja lokalizovanu kolekciju urina u retroperitoneumu, izvan urinarnog sistema. Iako relativno retki, urinomi prouzrokovani traumom predstavljaju velike dijagnostičke i terapijske izazove u pedijatrijskoj populaciji. Dijagnostika ultrasonografijom značajna je u prvobitnoj proceni ali kompjuterizovana tomografija i magnetno-rezonantni imidžing ipak pružaju jasniju diferencijaciju i informacije o samoj lokalizaciji. Strategija lečenja bazira se na prevenciji potencijalnih komplikacija i podsticanju oporavka urinarnog trakta. **Prikaz slučaja.** Predstavljamo prikaz slučaja sedamnaestogodišnjeg dečaka sa penetrantnom povredom abdomena. Reč je o pacijentu kod kojeg je načinjena promptna eksploracija abdomena kada su verifikovane i zbrinute manje laceracije kolona i slezine. Nakon otpusta pacijent se ponovo vraća na kliniku sa tegobama u vidu febrilnosti i bolova u trbuhu. Daljom dijagnostikom, inicijalno previđena povreda uretera i formiran urinom, okarakterisan je kao pseudocista pankreasa. Postoperativnom kompjuterizovanom tomografijom, cistografijom i retrogradnom pijelografijom jasno je izdiferencirano postojanje urinoma. **Zaključak**. Ovom atipičnom manifestacijom i prikazom slučaja cilj nam je bio da istaknemo važnost diferencijalne dijagnoze, kompleksnost abdominalnih povreda u pedijatrijskoj populaciji, kao i same dijagnostike i lečenja, sa akcentom na važnost multidisciplinarne strategije radi optimizacije ishoda lečenja.

Ključne reči: pseudocista pankreasa; urinoma; diferencijalna dijagnoza; povrede abdomena; ubodne rane; ureter; ishod lečenja; adolescent; CT; perkutana nefrostomija

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Introduction

A urinoma is an encapsulated collection of leaked urine, typically resulting from trauma, obstructive urinary pathologies, or iatrogenic surgical injuries [1–4]. Despite its rarity, timely recognition and treatment of urinomas are critical due to the potential for severe complications if left untreated. While usually associated with trauma or surgical complications, the presentation of a urinoma as a pseudocyst following abdominal injury is exceedingly rare. Urinomas pose diagnostic challenges due to their varied etiologies and clinical presentations. Identifying a urinoma requires a comprehensive understanding of its diverse origins, often necessitating a multidisciplinary diagnostic approach that includes imaging modalities and biochemical analyses. Ultrasonography is instrumental in the initial assessment by detecting free fluid collections. However, computed tomography (CT) and magnetic resonance imaging provide superior delineation of the urinoma's

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Abbreviations
CT – computed tomography
CECT – contrast-enhanced computed tomography
GU – Genitourinary

extent, localization, and potential complications, thus aiding in differential diagnoses. Treatment strategies for urinomas focus on addressing the underlying cause, mitigating potential complications, and promoting urinary tract healing [5, 6]. This case report details an atypical scenario where a patient, initially misdiagnosed with a pancreatic pseudocyst following abdominal trauma, subsequently developed a urinoma with intricate consequences. The case underscores the diagnostic challenges and the necessity for multiple interventions, highlighting the importance of accurate and timely diagnosis.

Case report

Initial examination and management

The 17-year-old patient was admitted with a stab wound to the abdomen. Upon arrival, the patient exhibited stable vital signs: a pulse rate of 89/min, blood pressure of 120/85 mmHg, and arterial oxygen saturation of 100%. Clinical assessment revealed a penetrating wound in the left hypochondrium with a protrudingomentum, which abdominal ultrasonography confirmed by detecting the presence of free fluid. An immediate exploratory laparotomy uncovered two abdominal wall wounds, including a minor splenic vessel injury and a 7 mm colonic perforation. Both the colonic perforation and the splenic vessel injury were surgically repaired with single sutures, and an abdominal drain was placed. Postoperatively, the patient was admitted to the intensive care unit, and the postoperative phase was uneventful. The drain was removed four days later and the patient was transferred to the abdominal surgery department. The remainder of his hospitalization stay was without fever or pain, and was discharged on the 12th postoperative day.

Postoperative complications, further diagnostics, and urinoma management

One week after discharge, the patient returned with a high fever and abdominal pain. Subsequent ultrasound imaging revealed dense free fluid in the pelvic area and a distinct formation (132x60 mm) in the upper left abdomen near the left kidney. He was readmitted for further monitoring and treatment. Follow-up ultrasound imaging revealed an encapsulated, oval-shaped fluid collection (140x80 mm) surrounding the pancreatic tail and another collection compressing the left kidney's pelvicalyceal system. A decision was made to perform a re-laparotomy. During the exploratory procedure, a tense bursa omentalis was noted, revealing a pseudocyst measuring 15x10 cm. The cyst was opened, and 400 ml of clear, yellowish fluid was obtained. Samples of this fluid were taken for microbiological and biochemical analysis. The posterior wall of the pseudocyst consisted of hyperemic pancreatic tissue, with no visible pancreatic lesions. Abdominal drains were placed in the Douglas' space, bursa omentalis, and the pseudocyst. The pseudocyst was initially considered to be a pancreatic cyst. Postoperatively, the patient was again placed in the intensive care unit with dual antibiotic therapy. During postoperative care, laboratory results showed increased inflammatory parameters, and an unusually large amount of clear fluid was observed in the drains, prompting a CT scan.

The CT scan correctly diagnosed a left-sided urinoma, which had caused a perirenal abscess and consequent grade III hydronephrosis. The diagnosis was confirmed through cystoscopy and retrograde pyelography, revealing a lesion in the proximal third of the left ureter. A urinary catheter was then introduced. Follow-up CT imaging showed ongoing communication between the proximal left ureter and the urinoma (94x49x67 mm) adjacent to the left kidney, prompting the placement of a percutaneous nephrostomy. The patient was discharged in stable condition, symptom-free, with a functioning nephrostomy after one month of hospitalization.

Follow up

Two months later, the patient was readmitted for further analysis and control diagnostic tests. Intravenous urography revealed a slight narrowing of the left ureter below the ureteropelvic junction, without any impediment to contrast flow. A decision was made to place a JJ stent through the nephrostomy. Three months later, both the JJ stent and nephrostomy were removed. The postinterventional course was uneventful, with complete resolution of all intra-abdominal collections and no further dilatation of the pelvic system.

Discussion

Genitourinary (GU) trauma is often overlooked in acute trauma settings because life-threatening injuries take precedence. However, GU trauma accounts for approximately 10% of all injuries seen in the emergency room. Ureteral trauma is particularly uncommon, constituting less than 1% of all urologic injuries [7, 8]. Urinoma can form as a result of collecting system disruption at any level from the calyces to the urethra [3]. Diagnosing ureteral injuries in acute trauma settings requires a high index of suspicion [7]. In our case, an initial laparotomy was performed due to evidence of intra-abdominal injury on ultrasound, the presence of increased intra-abdominal fluid, and blood loss. Although the laparotomy revealed splenic vessel and colonic perforations, the ureteric injury was overlooked.

Unfortunately, no single imaging modality is ideally suited to diagnose an acute ureteral injury. Although ultrasound is widely used in trauma cases, it has proven unreliable in evaluating ureteral injuries due to their small caliber and retro-

peritoneal location of the ureters. On ultrasound, a urinoma typically appears as an ellipsoid or crescent-shaped anechoic cyst adjacent to the kidney, without direct communication with it. According to the European Association of Urology guidelines, computed tomography (CT) and an intra-operative single-shot intravenous pyelogram (IVP) are the most useful diagnostic tools for ureteral injuries [7]. Well-established CT protocols for diagnosing urinoma involve scanning both the abdomen and the pelvis before and after administering 100-150 ml of contrast. Images are typically taken 5-20 min following contrast injection. When unexplained free intraperitoneal fluid is identified on a CT scan in a hemodynamically stable patient after trauma, management options include observation, diagnostic peritoneal lavage, diagnostic laparoscopy, and exploratory laparotomy. The advent of laparoscopy has enabled surgeons to diagnose or rule out intra-abdominal injuries in a minimally invasive manner [9]. Benefits of diagnostic laparoscopy compared with peritoneal lavage include accurate visualization of the source and extent of bleeding, as well as the potential for therapeutic intervention and repair of injured intra-abdominal structure [9]. In our case, the initial abdominal exploration did not reveal any genitourinary injury, nor was it expected, likely due to the lack of fluid accumulation and absence of urinary symptoms. Consequently, no further diagnostic procedures were indicated, and the patient was discharged from the hospital in stable condition.

The differential diagnoses for a cystic structure adjacent to the kidney include mesenteric and pancreatic cyst, enteric duplication cyst, renal tumor, ureteric duplication, and lymphangioma. Due to these varied possibilities, it is crucial to accurately identify the exact localization of the free fluid collection and properly classify it [9].

After the second-look laparotomy, the cyst was characterized as a pancreatic pseudocyst due to its localization and characteristics. A pancreatic pseudocyst is defined as a localized fluid collection, rich in amylase and other pancreatic enzymes, surrounded by a well-defined wall of fibrous tissue. The majority occur as a common complication of chronic pancreatitis, but they may also occur with abdominal trauma [10]. Both pancreatic cysts and urinomas can be clinically asymptomatic or may manifest later in the course of treatment with symptoms such as pain [8]. It is important to differentiate perinephric urinomas, the collection of urine surrounding the kidney, from other etiologies because urinomas can lead to various complications. The main differences between perinephric urinomas and other cysticic structures lie in their content and etiology. The fluid in urinomas typically has high creatinine levels and low glucose levels relative to serum, while pancreatic pseudocysts contain amylase and other pancreatic enzymes. Due to the location and structure of the cyst, the initial impression was that it was a pancreatic pseudocyst. However, postoperatively, the large amount of fluid drained raised suspicion of a urinary tract injury, which was later confirmed with CT and retrograde pyelography. As Ogreden et al. suggested, CT is adequate for definitive diagnosis of urinoma [3], but contrast-enhanced computed tomography (CECT) is the preferred modality, as contrast extravasation can be used to identify urinary leaks [5, 8, 13, 14]. Renal scintigraphy is also used in patients with compromised renal function, as it can diagnose preserved function in the residual renal parenchyma, identify the nature of the perinephric collection, and establish communication of this collection with the pelvicalyceal system. This provides a low radiation alternative to serial CECTs in follow-up [5]. According to the literature, ultrasound-guided percutaneous aspiration can confirm the diagnosis of a urinoma if the aspirated fluid shows elevated levels of creatinine and decreased levels of glucose relative to serum [13, 14]. In our case, the initial diagnosis was confirmed through cystoscopy and retrograde pyelography, which revealed a lesion in the proximal third of the left ureter, leading to the introduction of a urinary catheter. Follow-up CT imaging showed ongoing communication between the proximal left ureter and the urinoma, prompting the placement of a percutaneous nephrostomy.

Complications of urinomas include the risk of infection, paralytic ileus, abdominal and flank pain, and electrolyte imbalance [12]. Sterile urine in contact with the retroperitoneum can trigger an inflammatory response, whereas infected urine may lead to an acute abdomen, retroperitoneal abscess formation, and retroperitoneal fibrosis in later stages [3]. Overall, the presence of a urinoma is associated with irreversible ipsilateral renal dysfunction in 70% to 80% of cases [9].

Once a correct diagnosis of post-traumatic urinoma is established, the treatment strategy involves initially placing drains and, if needed, a percutaneous nephrostomy.

While many urinomas are small and resolve spontaneously, large and expanding urinomas often require intervention [5, 6]. The primary objective of ureteral repair is the preservation of renal function. Hence, the most important factor in the management of these injuries is to maintain drainage of urine from the kidney [7]. The American Urological Association Urotrauma Guidelines recommend urinary drainage via a ureteral stent, percutaneous nephrostomy tube, or both [14–18]. Compared to percutaneous nephrostomy, ureteral stents may offer advantages such as improved patient comfort, avoidance of additional catheter and urinary bag care, and reduced risk of dislodgment, especially in the pediatric population [12]. As suggested, we initially placed a ureteral stent, but later a nephrostomy was necessary to ensure effective drainage and healing.

A nephrostomy tube is usually a temporary measure with a positive prognosis, placed only until the urethral injury heals. The long-term prognosis for

patients with urinomas depends on several factors, but with prompt and appropriate treatment, most patients maintain normal renal function. Proper drainage can significantly reduce the risk of infection as well as the need for antibiotic administration. The risk of recurrence is low if the underlying cause is effectively addressed and treated. Most patients return to their normal activities and have a good quality of life following successful treatment of urinoma.

Conclusion

The uniqueness of this case lies in the initial misinterpretation of a urinoma as a pancreatic pseudocyst, highlighting the diagnostic challenges associated with such rare presentations. This atypical manifestation underscores the importance of differential diagnosis, especially in complex post-traumatic scenarios involving abdominal injuries in pediatric patients. For diagnosing of urinomas, the gold standard imaging modality is a computed tomography scan, with contrast-enhanced omputed tomography playing a crucial role in the differential diagnosis of other cystic formations and effectively identifying urinary leaks. The treatment strategy for urinomas primarily focuses on preserving renal function and preventing complications. Drainage is often unnecessary for small urinomas, as they may resolve spontaneously. However, for large, non-reabsorbed urinomas, and in cases where there is a risk of sepsis, drainage should be the treatment of choice. Early placement of drainage systems, such as ureteral stents, percutaneous nephrostomy tubes, or both, is crucial to prevent sepsis and other complications. In this case, the patient's management involved multiple surgical interventions, drainage procedures, and ultimately placement of the nephrostomy and JJ stent.

This case highlights the crucial role of a multidisciplinary approach in optimizing treatment outcomes for pediatric patients with traumatic abdominal injuries. Continuous follow-up imaging is also necessary to monitor and manage any persistent urinoma-related complications, ensuring a tailored and effective plan for the successful resolution of the condition.

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Case report
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RARE CASE OF UNILEAFLET MITRAL VALVE DIAGNOSED BY COMPUTED TOMOGRAPHY

REDAK SLUČAJ JEDNOLISNE MITRALNE VALVULE DIJAGNOSTIKOVAN KOMPJUTERIZOVANOM TOMOGRAFIJOM

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Summary

Introduction. Congenital malformations of the mitral valve encompass a broad spectrum of lesions, with an incidence of approximately 0.4% among patients with congenital heart diseases. **Case Report.** A 45-year-old female was admitted to our institution due to a confirmed mitral valve defect identified via echocardiographic examination. She presented with leg swelling and rapid fatigue. Her medical history includes systemic lupus erythematosus. Upon admission, she was in cardiopulmonary decompensation, with a systolic murmur detected in the mitral valve area, radiating towards the axilla. Transesophageal echocardiographic revealed severe mitral stenosis with moderate regurgitation, without clear visualization of the two cusps. Cardiac computed tomography confirmed a voluminous anterior mitral cusp and a hypoplastic posterior cusp, observed in diastole as a crescent-shaped, characteristic of a unicuspid mitral valve. Follow-up echocardiographic showed progression of mitral regurgitation with circumferential pericardial effusion, necessitating pericardiocentesis. Due to further hemodynamic instability, urgent surgical mitral valve replacement was indicated. The surgery proceeded without complications, but the immediate period was marked by exacerbation of renal impairment, requiring hemodiafiltration on several occasions. Following cardiological stabilization, the patient was transferred to the Nephrology Clinic for further management of renal insufficiency and systemic lupus. **Conclusion.** It is crucial to emphasize the significance of a multidisciplinary approach for each patient, with particular emphasis on detailed imaging diagnostics to definitively establish a congenital heart disease diagnosis.

Key words: Mitral Valve; Congenital Abnormalities; Tomography, X-Ray Computed; Echocardiography; Heart Valve Prosthesis Implantation; Signs and Symptoms; Hemodynamics; Diagnostic Imaging; Postoperative Complications; Renal Insufficiency

Sažetak

Uvod. Kongenitalne malformacije mitralne valvule predstavljaju širok spektar lezija, sa incidencijom od 0,4% među pacijentima sa kongenitalnom bolešću srca. **Prikaz slučaja.** Pacijentkinja starosti 45 godina je primljena u našu ustanovu zbog verifikovanog mitralnog defekta ehokardiografskim pregledom, što je bilo praćeno oticanjem nogu i brzim zamaranjem. Od komorbiditeta navodi sistemski lupus. Pri prijemu kardiopulmonalno dekompenzovana, sa auskultatorno verifikovanim sistolnim šumom u predelu mitralne valvule, koji propagira put aksile. Transezofagealnim ehokardiografskim pregledom verifikovana je teška mitralna stenoza sa umerenom regurgitacijom, bez jasne vizualizacije dva kuspisa. Kompjuterizovanim tomografijom srca verifikovano je postojanje voluminoznijeg anteriornog mitralnog kuspisa, dok je posteriorni kuspis hipoplastičan, što se u dijastoli videlo kao oblik polumeseca (karakteristika jednolisne mitralne valvule). Načinjen je kontrolni transtorakalni ehokardiografski pregled gde je evidentirana progresija mitralne regurgitacije, sa cirkularnim perikardnim izlivom, zbog čega je načinjena perikardiocenteza, ali usled dalje hemodinamičke nestabilnosti indikovana je urgentna hirurška zamena mitralne valvule. Kardiohirurška intervencija je protekla bez komplikacija, ali je neposredno postoperativno registrovana akutizacija bubrežne slabosti, zbog čega je načinjena hemodijafiltracija u nekoliko navrata. Nakon kardiološke stabilizacije, pacijentkinja je premeštena na Kliniku za nefrologiju radi daljeg tretmana bubrežne insuficijencije i sistemskog lupusa. **Zaključak.** Krucijalno je naglasiti značaj multidisciplinarnog pristupa kod svakog pacijenta, sa posebnim skretanjem pažnje na imidžing dijagnostiku kao definitivnu dijagnostičku metodu za uspostavljanje dijagnoze kongenitalne bolesti srca.

Ključne reči: mitralna valvula; kongenitalne abnormalnosti; CT; ehokardiografija; implantacija srčanog zaliska; znaci i simptomi; hemodinamika; dijagnostički imidžing; postoperativne komplikacije; bubrežna insuficijencija

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Abbreviations

LV – left ventricle
CHD – Congenital heart disease
MV – mitral valve
MR – mitral regurgitation
TTE – transthoracic echocardiography
TEE – transesophageal echocardiography
CT – computed tomography
CVVHDF – continuous veno-venous hemodiafiltration

Introduction

The mitral apparatus is a complex anatomical structure situated between the left atrium and left ventricle (LV). It comprises the annulus, and the anterior and posterior cusps, which are connected to the two papillary muscles of the LV via chordae tendineae, preventing valve prolapse during ventricular systole. Given the complexity of its anatomy and the importance of each segment, the integrity of the mitral apparatus is essential for adequate LV function.

Congenital heart disease (CHD) is the leading cause of mortality in infants, with anomalies of the heart and large blood vessels being the most common fetal abnormalities [1]. Congenital malformations of the mitral valve (MV) cover a wide spectrum of lesions, with an incidence of approximately 0.4% among patients with CHD, or 5 per 100,000 in the general population [2, 3]. These malformations can present in several forms, including parachute MV, double orifice MV, cleft MV, atresia, and unileaflet MV, with unileaflet MV being one of the rarest [4, 5]. Unileaflet MV typically diagnosed in early childhood and is generally incompatible with life due to the presence of severe mitral regurgitation (MR) [4]. In asymptomatic patients with unileaflet MV, severe hypoplasia of the posterior mitral cusp is often observed [6].

Patients with unileaflet MV experience symptoms due to severe MR, which manifests as rapid fatigue, dyspnea, inability to lie flat, palpitations, and pretibial edema. Auscultation over the MV reveals a pansystolic murmur that often radiates to the axilla. The diagnosis of unileaflet MV is usually made through clinical examination and transthoracic echocardiography (TTE), while transesophageal echocardiography (TEE) and cardiac computed tomography (CT) provide precise evaluation of the mitral apparatus.

Case Report

We present a case involving a 45-year-old female patient who was transferred to our institute from the Institute for Pulmonary Diseases of Vojvodina, where TTE revealed hypertrophic cardiomyopathy and combined mitral valve disease. The patient reported swelling of her legs over the past week, along with rapid fatigue upon mild physical exertion and difficulty breathing. Additionally, she had a persistent dry cough for the past month, for which she was prescribed systemic intravenous corticosteroid and antibiotic therapy. She had been treated for hypertension for several months. Other comorbidities included systemic lupus erythematosus accompanied by lupus rheumatoid arthritis, stage II renal insufficiency, hyperlipidemia, a history of smoking, and a family history of cardiac diseases, all risk factors for ischemic heart disease.

Upon admission to our institution, the patient was conscious, oriented, and communicative, with borderline hypertension (140/90 mmHg), a normal heart rate (80 bpm), and cardiopulmonary decompensation. Clinically, pretibial edema was observed, more pronounced in the left lower leg. Auscultation revealed bilaterally diminished breath sounds at the lung bases without other accompanying sounds, and a pronounced systolic murmur with radiation to the axilla was heard at the mitral area. Laboratory tests showed markedly elevated levels of NT-proBNP (21,663 pg/ml), increased levels of nitrogenous substances (urea 9.5 mmol/l, creatinine 135 μmol/l), and elevated inflammatory markers (C-reactive protein 53 mg/l, fibrinogen 10.7 g/l). Based on these findings, continuous intensive diuretic therapy was initiated along with empirical parenteral antibiotic therapy.

Transesophageal echocardiography revealed dilated LV with increased volume, severe mitral valve stenosis (MaxPg 56 mmHg/30 mmHg), and moderate MR. 4D reconstruction of the mitral valve did not clearly visualize the two cusps. Additionally, moderate tricuspid valve insufficiency with consequent pulmonary hypertension was noted. Cardiac CT was performed for a precise evaluation of the mitral valve, revealing a voluminous anterior mitral cusp while the posterior mitral cusp was not visualized, suggesting atresia. In diastole, the mitral orifice appeared crescent-shaped, consistent with a unileaflet mitral valve **(Figure 1).** Following all diagnostic procedures, a diagnosis of unileaflet mitral valve was established, warranting mitral valve replacement.

During the preoperative hospital course, the patient experienced intermittent febrile episodes with increased inflammatory markers, leading to the prescription of empirical parenteral antibiotic therapy. Due to significant orthopnea and tachypnea, non-invasive mechanical ventilation was applied several times, along with intensive parenteral diuretic and bronchodilator therapy. These symptoms subsequently improved, but due to right-sided pleural effusion, a pleural puncture was performed. Laboratory tests revealed an acute exacerbation of renal insufficiency, necessitating continuous venovenous hemodiafiltration (CVVHDF), which resulted in decreased levels of nitrogenous substances.

A follow-up TTE examination revealed the progression of MR along with circumferential pericardial effusion, with separation of the pericardial layers up to 2.2 cm, indicating impending tamponade. Consequently, pericardiocentesis was performed, evacuating 650 ml of hemorrhagic fluid. However, the patient's hemodynamic status deteriorated, necessitating an urgent transfer to the cardiac surgery operating room, where emergency mitral valve replacement with a mechanical bileaflet valve (St. Jude No. 23) was performed. The cardiac surgery proceeded without complications, with a total cardiac arrest time of 91 minutes and a cardiopulmonary bypass time of 103 minutes.

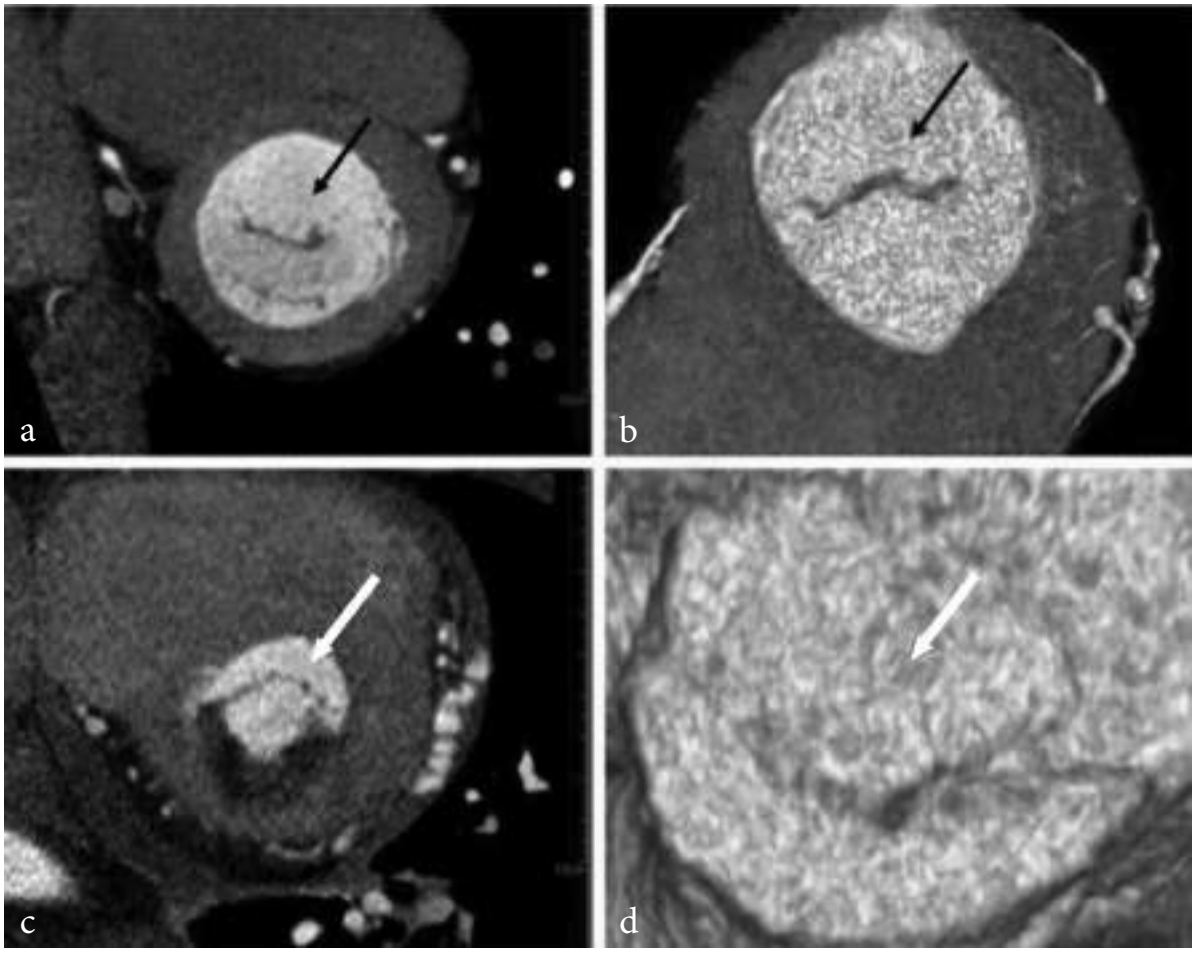

Figure 1. a) and b). Black arrow showing normal mitral valve – fish mouth shaped; **c) and d)** white arrow showing unileaflet mitral valve – crescent-shaped
Slika 1. a) i b) *Crna strelica je usmerena na mitralnu valvulu normalnog izgleda – oblika ribljih usta;* ***c) i d)*** *bela strelica pokazuje jednolisnu mitralnu valvulu naše pacijentkinje koja je oblika polumeseca*

In the immediate postoperative course, the patient was hemodynamically and rhythmically unstable, requiring high doses of vasopressor support. Arterial blood gas analysis revealed metabolic acidosis with elevated lactate levels. Based on hemodynamic parameters, inotropic support was initiated, gradually achieving hemodynamic stability. Due to significant pleural effusion detected on echocardiography and chest radiography, a left pleural drain was placed, yielding serous fluid.

After discontinuation of continuous sedation and stabilization of arterial blood gas exchange, weaning from mechanical ventilator support was initiated, and the patient was extubated on the third postoperative day. Febrile episodes prompted blood culture sampling, which returned negative results, while sputum culture was positive for Acinetobacter species, leading to antibiotic therapy according to the antibiogram.

Recurrent acute exacerbation of renal insufficiency with anuria and markedly elevated nitrogenous substance levels (urea 21.9 mmol/l, creatinine 317 μmol/l) necessitated postoperative CVVHDF on multiple occasions. Following complete stabilization of the cardiac condition, the patient was transferred to the University Clinical Center of Vojvodina, specifically to the Nephrology and Immunology Clinic, for further monitoring and treatment of renal insufficiency and systemic lupus erythematosus.

Conclusion

Although congenital heart diseases are most commonly detected in the neonatal period, some cases are identified later in life. Our case report illustrates such a scenario, where a congenital anomaly of the mitral valve was discovered in adulthood. Through a multidisciplinary and prompt approach, the patient was successfully managed from a cardiological perspective.

This case underscores the importance of a multidisciplinary approach for each patient, with particular emphasis on detailed imaging diagnostics to definitively establish a diagnosis of congenital heart disease.

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IN MEMORIAM
IN MEMORIAM

Prof. dr ERVIN GEBAUER
(1935–2023)

Napustio nas je prof. dr Ervin Gebauer, pedijatar, redovni profesor Medicinskog fakulteta u Novom Sadu, u penziji, redovni član Akademije medicinskih nauka SLD.

Prof. dr Ervin Gebauer rođen je u Baču, u uglednoj porodici farmaceuta. Školovanje je započeo u rodnom Baču, a nastavio u obližnjoj Bačkoj Palanci u kojoj je pohađao gimnaziju. Upisao je Medicinski fakultet Univerziteta u Zagrebu na kome je diplomirao 1960. godine. Nakon odsluženja obaveznog vojnog roka tokom koga je radio kao garnizonski lekar u Novom Pazaru, zapošljava se u Domu zdravlja Bač u kome radi u periodu 1962−1969. godine. Želja da pomogne rodnom gradu motivisala ga je da aktivno radi na poboljšanju zdravstvene zaštite i uslova života u opštini Bač. Učestvovao je u integrisa-nju i formiranju Doma zdravlja Bač za čijeg je direktora ubrzo imenovan. Sagledavajući potrebe stanovništva bačke opštine, dr Gebauer tokom svog direktorskog mandata otvara vanbolničko porodilište u Baču, a nedugo potom osniva i dečji dispanzer. Ljubav prema radu sa decom ga je nakon završenog tečaja iz pedijatrije usmerila ka pedijatriji kao konačnom profesionalnom opredeljenju, te dr Gebauer završava specijalizaciju iz pedijatrije 1969. godine na Klinici za dečje bolesti u Novom Sadu na kojoj se iste godine i zapošljava.

U Novom Sadu je osnovao i razvio Službu za dečju hematologiju i onkologiju kojom je uspešno rukovodio do penzionisanja. Željan znanja, dr Gebauer se povezao sa kolegama iz zemlje i inostranstva kako bi se sa svojim saradnicima dodatno edukovao i unapredio službu. Uspostavio je i održavao dobre veze, susrete i sastanke sa domaćim i stranim klinikama. Oblast posebnog stručnog interesovanja profesora Gebauera bila je hemostaza, prvenstveno hemofilija za čije je lečenje bio jedan od vodećih stručnjaka u bivšoj Jugoslaviji. Blisku saradnju u oblasti dečje hematologije i onkologije uspostavio je sa Univerzitetskom dečjom klinikom u Budimpešti što je dovelo do kasnijeg izbora profesora Gebauera za gostujućeg profesora Medicinskog fakulteta u Budimpešti što je uvek sa ponosom isticao. U oblasti pedijatrijske hematologije i onkologije usavršavao se u prestižnim inostranim ustanovama u Hamburgu, Cirihu, Bonu, Oslu, Londonu i Torontu.

Osim što je bio veoma uspešan i poznat lekar, profesor Gebauer je bio posvećen i naučnom radu i univerzitetskoj karijeri. Magistarski rad odbranio je na Medicinskom fakultetu u Zagrebu 1969. godine, a doktorsku disertaciju na Medicinskom fakultetu u Novom Sadu 1972. godine. Akademsku karijeru započeo je na Medicinskom fakultetu u Rijeci, gde je nakon odbranjenog habilitacionog rada 1974. godine izabran za naslovnog docenta. Ubrzo prelazi na Medicinski fakultet u Novom Sadu gde je izabran u zvanje docenta i napredovao do zvanja redovnog profesora. Tokom karijere bio je i šef Katedre za pedijatriju. Bio je nosilac više naučnoistraživačkih projekata i autor velikog broja radova objavljenih u međunarodnim i domaćim časopisima, urednik dva udžbenika iz pedijatrije i autor monografije *Bolesti krvarenja u dece*.

Aktivno je učestvovao u radu stručnih udruženja, a poseban doprinos dao je radu Srpskog lekarskog društva – Društva lekara Vojvodine čiji je član od 1962. godine. Bio je predsednik novosadske podužnice SLD-DLV, predsednik i član Predsedništva Sekcije za hematologiju i transfuziologiju, pedijatriju, trombozu i hemostazu, istoriju zdravstvene kulture. Kao istaknuti stručnjak u svojoj oblasti prof. Gebauer je bio

uključen u rad Kooperativne grupe za dečju hematologiju i onkologiju od osnivanja 1977. godine, a u dva mandata je bio i njen predsednik. Takođe je bio dugogodišnji predsednik Naučnog odbora za hemolitiku i hemostazu Srbije. Od 2002. godine je redovni član Akademije medicinskih nauka SLD u čijem je radu aktivno i sa velikim zadovoljstvom učestvovao. U više mandata je bio član uređivačkih odbora časopisa *Medicinski pregled* i *Bilten za transfuziologiju*. Za predan rad u SLD-DLV nagrađen je sa više priznanja. Bio je član više prestižnih međunarodnih stručnih udruženja (*Societe Internationale de Oncologie Pediatrique* − SIOP, *World Federation of Hemophilia* – WFH, *International Society on Thrombosis and Hemostasis* – ISTH, ...).

Profesor Gebauer je bio veoma obrazovan čovek, širokih interesovanja. Bio je poliglota, govorio je mađarski, nemački i engleski jezik. Kao čovek, bio je blage naravi, tolerantan i odmeren, zbog čega su ga naročito cenili saradnici i studenti. Deca su ga volela, a roditelji uvažavali.

Profesor dr Ervin Gebauer preminuo je Novom Sadu, a sahranjen je u Baču. Neka mu je večna slava!

Prof. dr Jovanka Kolarović

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4. Prethodna ili kratka saopštenja – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

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8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

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Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

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Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

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Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

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Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings, MeSH.*

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

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Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

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U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

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Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

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Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

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Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

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Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

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Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

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6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

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Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.