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RISK FACTORS FOR THE FORMATION OF ARTERIOVENOUS FISTULA THROMBOSIS IN PATIENTS TREATED WITH CHRONIC HEMODIALYSIS

FAKTORI RIZIKA ZA NASTANAK TROMBOZE ARTERIOVENSKE FISTULE KOD BOLESNIKA LEČENIH HRONIČNIM HEMODIJALIZAMA

Mira NOVKOVIĆ[1, 2], Violeta KNEŽEVIĆ[2, 3] and Lada PETROVIĆ[2, 3]

Summary

Introduction. Complications related to vascular access, alongside cardiovascular diseases, constitute the primary cause of hospitalization among patients undergoing hemodialysis. Thrombosis stands out as the most prevalent cause of arteriovenous fistula dysfunction. The research aimed to identify the risk factors contributing to thrombosis formation of the first arteriovenous fistula. **Material and Methods.** The study spanned one year and involved 40 patients who initiated hemodialysis through their first arteriovenous fistula at the University Clinical Centre of Vojvodina. The parameters analyzed included demographic, biochemical, and clinical factors, as well as the therapy given. **Results.** Among the 40 patients, 67% were male. The majority (57.5%) were aged over ≥ 60 years. Hypertension was the most prevalent comorbidity, affecting 35% of patients. Arteriovenous fistula thrombosis was diagnosed in 32% of patients. A logistical regression model was employed to determine predictors of arteriovenous fistula thrombosis. The analysis revealed that the patients with a body mass index greater than > 25 kg/m^2, had a 1.5 times higher risk of thrombosis formation. Similarly, individuals with blood pressure exceeding > 140/90 mmHg had nearly a twofold increased risk, while those in the 45-59 age group had a fourfold higher risk. Patients who received anticoagulant therapy before arteriovenous fistula formation had a 16 times lower risk of thrombosis, and nearly 33 times lower risk with the application of angiotensin–converting–enzyme inhibitors/angiotensin II receptor blocker after arteriovenous fistula formation. **Conclusion.** Significant predictors of thrombosis formation of the first arteriovenous fistula among hemodialysis patients included body mass index greater than > 25 kg/m^2, blood pressure values exceeding > 140/90 mmHg, and age group of 45 – 69 years.

Key words: Arteriovenous Fistula; Thrombosis; Risk Factors; Renal Dialysis; Treatment Outcome

Sažetak

Uvod. Komplikacije vaskularnih pristupa, pored kardiovaskularnih bolesti predstavljaju vodeći uzrok hospitalizacija kod bolesnika koji se leče hemodijalizama. Tromboza je najčešći uzrok afunkcije arteriovenske fistule. Cilj ovog istraživanja bio je da se utvrde faktori rizika za nastanak tromboze prve arteriovenske fistule. **Materijal i metode.** Istraživanjem u trajanju od godinu dana obuhvaćeno je 40 bolesnika koji su započeli hemodijalizu preko prve arteriovenske fistule u Univerzitetskom kliničkom centru Vojvodine. Analizirani su demografski, biohemijski, klinički parametri i primenjena terapija. **Rezultati.** Od ukupno 40 bolesnika, 67% su bili muškog pola. Najzastupljenija starosna kategorija od 57,5% bila je ≥ 60 godina. Od komorbiditeta hipertenzija je na prvom mestu sa 35%. Tromboza arteriovenske fistule dijagnostikovana je kod 32% bolesnika. Radi utvrđivanja prediktora tromboze arteriovenske fistule urađen je logistički regresioni model koji je pokazao da su bolesnici sa indeksom telesne mase > 25 kg/m² imali 1,5 puta veću šansu za nastanak tromboze, skoro dva puta veću šansu sa krvnim pritiskom > 140/90 mmHg i četiri puta veću šansu za starosnu kategoriju 45−59 godina. Bolesnici koji su bili na antikoagulantnoj terapiji pre kreiranja arteriovenske fistule imali su 16 puta manju šansu za nastanak tromboze i čak 33 puta manju šansu za nastanak tromboze sa primenom inhibitora angiotenzin–konvertujućeg enzima/blokatora receptora za angiotenzin II posle kreiranja arteriovenske fistule. **Zaključak.** Značajni prediktori nastanka tromboze prve arteriovenske fistule kod bolesnika na hemodijalizi bili su: indeks telesne mase > 25 kg/m², vrednost krvnog pritiska > 140/90 mmHg i starosna kategorija 45−59 godina.

Ključne reči: arteriovenska fistula; tromboza; faktori rizika; hemodijaliza; ishod lečenja

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Abbreviations

CKD – chronic kidney disease
AVF – arteriovenous fistula
BMI – body mass index
DM – diabetes mellitus
HD – hemodialysis
ARB – angiotensin II receptor blockers
TT – thrombin time
PT – prothrombin time
OR – odds ratio
CRP – C-reactive protein
CI – confidence intervals
ACE – angiotensin-converting enzyme

Introduction

In terminal stadium chronic kidney disease (CKD), it is necessary to commence healing with one of the kidney function replacement methods: hemodialysis (HD), peritoneal dialysis, or kidney transplant [1]. Arteriovenous fistula (AVF) is advocated as the preferred vascular access option for HD due to its longevity and fewer complications compared to other vascular access types [2]. However, despite having the fewest complications, arteriovenous fistula can still be associated with intraoperative, early, and later postoperative complications [3]. Thrombosis, along with stenosis, ranks among the most common later complication of AVF, with thrombosis incidence ranging from 17% to 25%. It stands as one of the leading causes of AVF dysfunction, necessitating the placement of a dialysis catheter to continue HD. Patients with hematocrit levels higher than 40%, lower level of protein C and S, and confirmed mutations of factors V Leiden and lupus anticoagulant are at higher risk of thrombosis [4]. The aim of this study was to identify the risk factors contributing to thrombosis formation in the first arteriovenous fistula. We also expected that arteriovenous fistula thrombosis would occur more frequently in female patients aged over 60 years, and that the most common clinical parameters such as diabetes mellitus and hyperlipidemia would be prevalent risk factors.

Material and Methods

The retrospective study was conducted at the Hemodialysis Department of the Clinic of Nephrology and Clinical Immunology of the University Clinical Centre of Vojvodina from 2017 to 2018. The study period predates the Covid-19 pandemic, as patients were subsequently transferred to other satellite dialysis centers and a new COVID hospital, resulting in incomplete patient data access. The study included 40 patients who initiated HD with their first AVF during 2017, and their data were followed until the end of 2018, kidney transplant, transfer to another dialysis center, or death. Patients permanently transferred from peritoneal dialysis to HD within the first year were included. The patients underwent dialysis 1-3 times a week for 4 hours, utilizing bicarbonate on polysulfonic capillary membranes with a surface ranging from 1.1 to 1.3 m^2 and a blood flow rate of 300 ml/min. Inclusion criteria comprised age ranging from 18 to 80 years, initiation of HD with the first created AVF, and absence of evidence of secondary hemophilia or heparin-induced thrombocytopenia. Patients immediately transferred to another satellite dialysis center upon initiating treatment at the Clinical Centre of Vojvodina, as well as those with diagnosed malignant disseminated disease, were excluded from the study. Through the research period, the following biochemical parameters were analyzed monthly: complete blood analyses, hemostatic mechanism, prothrombin time (PT), thrombin time (TT), fibrinogen (g/l).

Data analyzed every three months included nutritional, lipid, and inflammation parameter: albumin (g/l), total cholesterol, triglycerides, and C-reactive protein (CRP) (mg/l). AVF functionality was evaluated through clinical examination and Doppler ultrasound of the upper extremities. Complete blood analyses with a differential blood count were conducted on SYSMEX XN-1000 apparatus employing the flow cytometry method and commercial kits from the same manufacturer. Serum albumin concentration was determined using a photometric color test on the OLYMPUS analyzer with Beckman Coulter kits (Ireland). Total cholesterol and triglycerides were measured using standard enzyme procedure with reagents from BIOMERIEUX. Serum CRP concentration was determined through immune turbidimetric testing on the Siemens Dimension Xpand analyzer with commercial tests from Siemens. Parameters of the hemostatic mechanism (PT, TT, fibrinogen) were determined using a coagulant method on Siemens apparatus. HD adequacy was analyzed based on the Kt/Vsp index, calculated using the formula: $Kt/Vsp = \ln(C2/C1 - 0.008 \times T) + (4 - 3.5 \times C2/C1) \times UF/W$, where: C1 represents the redialysis value of urea (mmol/l), C2 represents the post-dialysis value of urea (mmol/l), T is the dialysis time span (hours), UF is the inter-dialysis proceeds (liters), W is the post-dialysis body mass (kg).

Statistical data analyses included descriptive statistics methods, with numerical data presented as mean values (arithmetic mean) and measures of variability (standard deviation), while categorical data were presented as frequencies and percentages. Differences in analyzed parameters between two or more groups were assessed using appropriate Student t-test, actually nonparametric Mann-Whitney test, and Kruskal-Wallis tests. Differences in categorical data were assessed using the chi-square test. Multiple analyses utilized binary logistic regression models, and coefficient significance assessed using the Wald test, odds ratio (OR), and 95% confidence intervals (CI). Values of $p<0.05$ were considered statistically significant.

Results

This research included 40 patients, with 27 (67%) being men. The oldest age category (>60) was the most prevalent. Hypertension was the most common comorbidity (35%), followed by diabetes mellitus (25%), glomerulonephritis (10%), polycystic kidney disease (10%), tubulointerstitial nephritis (5%), and other co-

Table 1. Demographic, clinical parameters and therapy of patients after the first AVF creation
Tabela 1. *Demografski, klinički parametri i terapija bolesnika posle kreiranja prve AVF*

	N/*Br.*
Age/*Starost*	
30-44	4 (10.0)
45-59	13 (32.5)
≥60	23 (57.5)
Comorbidities/*Komorbiditeti*	
Diabetes mellitus/*Dijabetes melitus*	10 (25)
Arterial hypertension/*Arterijska hipertenzija*	14 (35)
Hyperlipidemia/*Hiperlipidemija*	7 (18)
Glomerulonephritis/*Glomerulonefritis*	4 (10)
PKD/*PBB*	4 (10)
TIN/*TIN*	2 (5)
Other diseases/*Drugo oboljenje*	6 (15)
Therapy/*Terapi*ja	
UFH	6 (15)
LMWH	22 (55)
Statins/*Statini*	19 (47.5)
ACE/ARBs	17 (42.5)
ESA	11 (27.5)
Without therapy change/*Bez promene terapije*	14 (35)

Legend: UFH – unfractionated heparin; LMWH – low-molecular-weight heparin; ACE –angiotensin-converting enzyme; ARBs – angiotensin II receptor blockers; ESA – erythropoietin-stimulating agent; PKD – Polycystic kidney disease, TIN –tubulointerstitial nephritis
Legenda: UFH − nefrakcionisani heparin; LMWH − niskomolekularni heparin; ACE − angiotenzin-konvertujući enzim; ARB − blokatori receptora angiotenzina II; ESA − eritropoetin; PBB − policistična bolest bubrega, TIN − tubulointersticijalni nefritis

Table 2. Laboratory and clinical parameters of patients with and without thrombosis
Tabela 2. *Laboratorijski i klinički parametri bolesnika sa trombozom i bez nje*

	Patients with thrombosis *Bolesnici sa trombozom* N/*Br.* 13	Patients without thrombosis *Bolesnici bez tromboze* N/*Br.* 27
Blood pressure/*Krvni pritisak* (mmHg) (N/*Br.* %)		
>140/90 mmHg	9 (30)	21 (70)
<140/90 mmHg	4 (40)	6 (60)
BMI/*Indeks telesne mase* (kg/m^2) (n%)		
Malnutrition/*Pothranjenost*	0 (0)	2 (100)
Normal nutrition/*Normalna uhranjenost*	4 (30.8)	9 (69.2)
Pre-obesity/*Predgojaznost*	6 (37.5)	10 (62.5)
Obesity/*Gojaznost*	3 (33.3)	6 (66.7)
Lab parameters[a] *Laboratorijski parametri*[a]	Arithmetic mean *Aritmetička sredina*	Standard deviation *Standardna devijacija*
Hemoglobin/*Hemoglobin* (g/l)	89.08 ± 27.11	101.59 ± 9.55
Erythrocytes/*Eritrociti* (x 10^{12})	3.01 ± 0.33	3.23 ± 0.39
Plateles/*Trombociti* (x 10^9)	196.31 ± 78.91	206.48 ± 71.47
Albumins/*Albumini* (g/l)	39.15 ± 6.46	36.74 ± 7.73
CRP/C *reaktivni protein* (mg/l)	9.63 ± 5.96	10.18 ± 9.87
Cholesterol/*Holesterol* (mmol/l)	4.39 ± 1.07	4.28 ± 0.96
Triglycerides/*Trigliceridi* (mmol/l)	1.87 ± 1.08	1.68 ± 1.17
PT (R)	0.87 ± 0.82	0.69 ± 0.56
TT (R)	0.72 ± 0.67	0.63 ± 0.49
Fibrinogen/*Fibrinogen* (g/l)	5.18 ± 2.67	5.03 ± 1.71

Legend: CRP – C-reactive protein; PT – Prothrombin time; TT – Thrombin time;
Legenda: CRP − C-reaktivni protein; PT − protrombinsko vreme; TT − trombinsko vreme;

morbidities (15%). After the creation of AVF, low molecular heparin therapy was initiated in 55% of patients, statins in 47.5%, and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) in 42.5% of patients **(Table 1).**

Among patients with AVF thrombosis, 30% had blood pressure values >140/90 mmHg, while 40% of patients had values <140/90 mmHg. Additionally, 33.5% of pre-obese patients and 33.3% of obese patients experienced thrombosis. Patients with AVF thrombosis

Table 3. Predictors of AVF thrombosis
Tabela 3. *Prediktori tromboze arteriovenske fistule (AVF)*

Independent factors *Nezavisni faktori*	B	Wald	p/*p*	OR	95% CI za OR	
					Lower/*Nizak*	Upper/*Visok*
Gender/*Pol* Male/*Muški* Female/*Ženski*	-0.863	1.149	0.284	0.422	0.087	2.045
Age/*Starost* 30-44 45-59 ≥60	 1.472 0.788	 1.382 0.487	 0.040* 0.485	 4.366 2.197	 0.020 0.050	 2.671 4.165
Constant/*Konstanta*	0.432	0.154	0.695	1.540		
Hemoglobin/*Hemoglobin* (g/l)	-0.050	1.537	0.215	0.951	0.879	1.029
Erythrocytes/*Eritrociti* (x 10^{12})	-1.759	1.717	0.190	0.172	0.012	2.392
Plateles/*Trombociti* (x 10^{9})	-0.007	0.877	0.349	0.994	0.980	1.007
Albumins/*Albumini* (g/l)	0.050	0.809	0.368	1.051	0.943	1.173
CRP (mg/l)/*CRP* (mg/l)	0.023	0.184	0.668	1.024	0.920	1.139
Cholesterol/*Holesterol* (mmol/l)	0.721	1.044	0.307	2.056	0.516	8.196
TG/*TG* (mmol/l)	-0.223	0.877	0.684	0.800	0.273	2.341
PT (R)/*PT (R)*	-0.566	0.169	0.681	0.568	0.038	8.456
TT (R)/*TT (R)*	-1.487	1.074	0.300	0.226	0.014	3.762
Fibrinogen/*Fibrinogen* (g/l)	0.312	1.611	0.204	1.367	0.844	2.214
Constant/*Konstanta*	5.524	0.876	0.349	250.519		
Comorbidities/*Komorbiditeti*	0.566	2.828	0.039*	1.761	0.911	3.404
DM Yes/No/*Da/Ne*	0.637	0.524	0.469	2.529	0.094	2.970
HLP Yes/No/*Da/Ne*	0.447	0.297	0.586	1.564	0.313	7.809
OAC[a] Yes/No/*Da/Ne*	-2.793	4.159	0.041*	0.061	0.004	0.897
OAC[b] Yes/No/*Da/Ne*	-0.081	0.003	0.959	0.823	0042	0.140
APT[b] Yes/No/*Da/Ne*	-0.304	0.065	0.799	0.738	0.071	7.696
ACE/ARB[b] Yes/No/ *Da/Ne*	-3.490	4.397	0.036*	0.030	0.001	0.796
Statins[b] Yes/No/*Statini Da/Ne*	-0.052	0.609	0.435	0.592	0.237	8.352
Constant/*Konstanta*	0.415	0.050	0.824	1.515		
BP/*KP* (mmHg) ≥140/90 <140/90	0.304	0.146	0.002*	1.738	0.155	3.508
Kt/V	-1.234	0.510	0.475	0.291	0.010	8.605
BMI/*Indeks telesne mase* (kg/m^2) <25 >25	0.439	0.363	0.047*	1.551	0.372	6.463
Number of HDs a week/*Broj Hd nedeljno*	0.613	0.659	0.862	1.864	0.166	4.496
Constant/*Konstanta*	-1.597	0.291	0.590	0.202		

Legend: CRP – C-reactive protein; ACE/ARBs – Angiotensin-converting enzyme/angiotensin II receptor blockers; BMI – body mass index; APTT – Activated partial thromboplastin time; PT – Prothrombin time; TT – Thrombin time; HD – hemodialysis; BP – blood pressure; AVF – arteriovenous fistula; TG – triglycerides; DM – Diabetes mellitus; HP – hyperlipoproteinemia; OAC – anticoagulation therapy; APT – antiplatelet therapy
[a]before AVF creation; [b]after AVF creation
Legenda: CRP – C-reaktivni protein; ACE/ARB – angiotenzin-konvertujući enzim/blokatori angitenzin II receptora; BMI – indeks telesne mase; APTT – aktivirano parcijalno tromboplastinsko vreme; PT – protrombinsko vreme; TT – trombinsko vreme; HD – hemodijaliza; KP – krvni pritisak; AVF – arteriovenska fistula: TG – trigliceridi; DM – dijabetes melitus; HP – hiperlipoproteinemija; AOK – antikoagulantna terapija; AKS – antiagregaciona terapija; CI – interval poverenja; PR – odds ratio
[a]pre kreiranja AVF; [b]posle kreiranja AVF

exhibited significantly lower hemoglobin values (89.08 +27.11 vs. p=0.030) compared to those without thrombosis **(Table 2).**

Table 3 displays the predictors of AVF thrombosis. Patients aged 45-59 years had a fourfold higher chance of developing AVF thrombosis (OR = 4.366, 95% CI:0.020 - 2,671, p=0.040) compared to the youngest patients (30-44 years old). To identify predictors of AVF thrombosis initiation, a multivariable logistic regression analysis was performed with AVF thrombosis as the dependent parameter and hemoglobin, erythrocytes, platelets, albumin, CRP, cholesterol, triglycerides, PT, TT, and fibrinogen as independent variables.

Higher PT values were associated with a nearly twofold smaller chance of AVF thrombosis development (OR=0.568, 95% CI:0.038-8.456), while higher TT values were associated with approximately 4.5 times smaller chance (OR=0.226, 95% CI:0.014-3.762). An increase in fibrinogen values was associated with a nearly 1.4 times higher chance of thrombosis development (OR=1.367, 95% CI:0.844-2.214). Moreover, an increase in the number of comorbidities was associated with an almost twofold higher chance of AVF thrombosis (OR=1.761, 95% CI:0.911-3.404, p=0.039). The use of anticoagulant therapy before AVF creation decreased the chance of thrombosis by 16 times (OR=0.061, 95% CI:0.004-897, p=0.031), while the use of ACE/ARB upon AVF creation decreased the chance by 33 times (OR=0.030, 95% CI:0.001-796, p=0.036). Patients with blood pressure ≥140/90 mmHg had almost double the chance of developing AVF thrombosis (OR=1.738, 95% CI:0.155–3.508 p=0.002), while pre-obese and obese patients (BMI >25 kg/m^2) had a 1.5 greater chance of thrombosis (OR=1.551; 95% CI:0.372–6.463, p=0.047) **(Table 3).**

Discussion

In our research, we analyzed the influence of potential independent risk factors on the development of thrombosis in the first AVF. When considering the influence of gender on the creation of AVF thrombosis, our findings did not reveal a significant difference between men and women. This contrasts the previous research where AVF complications were predominantly associated with female patients, as demonstrated in various studies including that of Rodriguez et al., which involved 1033 patients over 13 years [5]. However, a doctoral thesis by Jankovic A. conducted an 18-month study at the Clinical Hospital Center Zvezdara in Belgrade, which included 314 patients, and concluded that AVF complications were more prevalent among male patients [6]. Considering that the latter research studies were of non-homogenized types, with varying designs and time span, it is not surprising that different results were observed. Research findings regarding the impact of age on AVF function were not consistent with previous studies. Two studies indicated that age over 65 years resulted in poorer AVF function and suggested earlier planning of vascular access [5, 7]. In contrast, Jankovic A.'s results did not demonstrate a significant impact of age on the development of AVF complications [6]. This aligns with the research by Lock et al., who followed AVF function for six months with 248 patients under 65 year old and 196 patients over 65 year old, finding no difference between these groups. Therefore, they concluded that age should not influence the function and decision-making regarding AVF creation [8]. Although more than 50% of our patients with AVF thrombosis were aged 60 years or older, upon comparison across age groups, it was determined that patients aged 45-59 years had a fourfold greater chance of developing AVF thrombosis, which is significantly more compared to the youngest patients (30-44 years old). In our research, when examining the impact of laboratory parameters on the development of AVF thrombosis, the only significant finding was lower hemoglobin values in patients with thrombosis compared to those without thrombosis. Given that thrombosis accounts for 80% of AVF dysfunction cases, the pharmacological prevention of thrombosis is crucial. This involves the use of antithrombotic medications such as acetylsalicylic acid, clopidogrel, dipyridamole, or parenteral anticoagulants (low molecular weight and unfractionated heparin). Opinions regarding the application of anticoagulant therapy vary, but based on existing research, it can be concluded that anticoagulant therapy in AVF patients contributes to thrombosis prevention and the long-term functionality of AVF without the risk of bleeding [9]. The results of our research revealed that after AVF creation, 55% of patients were prescribed low molecular weight heparin therapy, 47.5% were prescribed statins, and 42.5% were prescribed ACE inhibitors. Before AVF creation, 75% of patients were not receiving anticoagulant therapy, 15% received anticoagulant therapy for up to a year, and 10% received it for more than a year. One in four patients was on some form of anticoagulant therapy before AVF creation. The logistic regression model demonstrated that patients who received anticoagulant therapy before AVF creation had significantly lower chance (16 times less) of developing thrombosis compared to those who did not receive this therapy. Furthermore, patients who were prescribed ACE/ARB upon fistula creation had an even greater reduction in the risk of AVF thrombosis, with a 33 times lower chance. Filipov P., in his doctoral thesis, conducted a five-year study involving 121 patients and found that AVF thrombosis occurred in 17.4% of patients. Among the 40 patients not taking medication, thrombosis occurred in 30% of cases, whereas in the group receiving antithrombotic therapy, thrombosis occurred in only 9.5% of cases [9]. These results highlight the variability in study outcomes and the need for precise guidelines on medication use to maintain AVF patency. In a two-year retrospective study involving 349 patients, none of the cardiovascular drugs including antiplatelet agents, dipyridamole and others demonstrated a positive effect on maintaining AVF patency. How-

ever, contrasting results were observed in a 10-year study involving 34354 patients with short-lasting AVF (≤1 year) and long–lasting AVF (>1 year). The study indicated a significant reduction in the risk of AVF failure with an increase in the cumulative daily dosage of antiplatelet drugs [10]. Similarly, a multicenter study involving 338 patients did not examine the dosage of antiplatelet drugs but showed that their use for 30 to 90 days after AVF creation significantly prolonged its duration, helping to overcome the period of common expected complications [11]. Among the investigated clinical predictors, an increase in the number of comorbidities was shown to significantly increase the risk of AVF thrombosis. Any additional comorbidity doubled the likelihood of AVF thrombosis development. Among the patients with DM, AVF thrombosis occurred in 22% of cases, a condition that, along with hyperlipidemia, was present in over 50% of patients. Our research findings indicate that patients with DM had a 2.5 times greater chance of developing AVF thrombosis, although this association did not reach statistical significance. Various studies have yielded differing results regarding the impact of DM on the function and complication development of arteriovenous fistula [6]. Alongside DM, hyperlipidemia represents another common cause of AVF thrombosis. In our study, hyperlipidemia was present in 18% of patients, and these patients had a 1.5 times greater chance of developing thrombosis compared to others, although this association did not reach statistical significance. Previous researched studies have shown varied results [3, 12]. Our patients were analyzed for HD parameter impact on AVF thrombosis development. We found that 40% of patients had a BMI of 25–29.9 kg/m^2, and 22.5% had a BMI ≥30 kg/m^2 among patients with thrombosis. Pre-obese and obese patients (BMI >25 kg/m^2) had a 1.5 times greater chance of developing AVF thrombosis. For obese patients, decreased AVF function may result from heavy cannulation due to deeply situated blood vessels. In such cases, AVF with surface transposition of arterialized vein is typically the first choice, followed by arteriovenous graft creation or the placement of a long-lasting dialysis catheter if unsuccessful [13]. Jemcov T., et al. in a two-year study involving 122 patients, found a six times higher risk of poor AVF function in malnourished and obese patients [14]. However, Lee et al. in a three-year survey of 173 patients did not find a significant effect of BMI on AVF outcomes [15]. Additionally, a study by Chan et al. indicated that only patients with BMI >35 kg/m² had poor AVF maturation [16]. Arterial blood pressure values are another risk factor for AVF thrombosis development. We analyzed both pre-dialysis and post-dialysis arterial blood pressure values. Pre-dialysis arterial blood pressure values >140/90 mmHg were present in 77.5% of patients, and among patients with AVF thrombosis, 69.2% had pre-dialysis pressure values of >140/90 mmHg. Those patients had nearly twice the significantly higher chance of developing AVF thrombosis compared to those with values of <140/90 mmHg. Siddiquia et al. also concluded that hypertension significantly impacts thrombosis development and weakens AVF function [17]. In contrast to our results, the cohort study by Kim et al. did not confirm the negative effect of arterial hypertension on AVF thrombosis development [18]. The hypothesis that arteriovenous thrombosis most often occurs in patients over 60 years of age was confirmed, as well as the finding that the dominant clinical parameters, such as DM and hyperlipidemia, are significant risk factors for thrombosis occurrence.

Conclusion

Significant predictors for arteriovenous fistula thrombosis development included a body mass index >25 kg/m², an increase in number of comorbidities, blood pressure >140/90 mmHg, and age group 45-59 years old. We found that the application of anticoagulant therapy before arteriovenous fistula development and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers after arteriovenous fistula development can significantly decrease the chance for arteriovenous fistula thrombosis development.

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SOCIODEMOGRAPHIC CHARACTERISTICS AND SMOKING-RELATED HABITS AMONG PARTICIPANTS IN A LUNG CANCER SCREENING PROGRAM IN VOJVODINA, SERBIA

SOCIODEMOGRAFSKE KARAKTERISTIKE I NAVIKE U VEZI SA PUŠENJEM UČESNIKA SKRININGA ZA RANO OTKRIVANJE RAKA PLUĆA U VOJVODINI, SRBIJA

Mirjana KOLUNDŽIĆ[1] and Snežana BOJANIĆ[2]

Summary

Introduction. Lung cancer ranks as the second most common cancer among women and the leading cancer among men in Serbia. This study aimed to analyze smoking-related habits among participants in a lung cancer screening program. **Material and Methods.** The cross-sectional study was conducted between September 29, 2020 and June 9, 2023. Relevant database records containing information on socio-demographic characteristics of patients treated at the Primary Healthcare Center Novi Sad were analyzed. Socio-demographic characteristics (age, gender, level of formal education), and smoking related habits, were obtained through an electronic questionnaire, specially designed for the purpose of the project. **Results.** Out of 2,460 respondents, 58.9% were females. The average age of the respondents was 63.7±6.8 years. The majority of the participants were smokers (83.3%). Nearly half (48.7%) considered quitting smoking in the previous six months, while 24% considered smoking cessation within the next 30 days. Participants frequently concerned about the risk of lung cancer development were more willing to quit smoking compared to those less concerned (33.3% vs. 16.2%, p<0.001). **Conclusion.** The study concludes that there is a low level of personal decisions to quit smoking, concern for one's health and insufficient awareness of the risks of lung cancer development. Physicians working in the primary healthcare settings should take a more proactive role in smoking cessation initiatives.

Key words: Lung Neoplasms; Primary Health Care; Smoking; Habits; Mass Screening; Demography; Health Knowledge, Attitudes, Practice

Sažetak

Uvod. Karcinom pluća je na drugom mestu po učestalosti karcinoma kod žena, a najčešći je kod muškaraca u Republici Srbiji. Cilj istraživanja bio je analiziranje navika (aktuelne i bivše) u vezi sa pušenjem kod učesnika skrining programa na karcinom pluća. **Materijal i metode.** Istraživanje je sprovedeno u vidu studije preseka u periodu 29. 9. 2020−9. 6. 2023. godine. Skrining karcinoma pluća primenom *low-dose computed tomography* sprovodi se u Institutu za plućne bolesti Vojvodine, a u odabir ispitanika za skrining uključen je Dom zdravlja Novi Sad. Za potrebe ovog skrining programa kreirana je baza podataka. Demografski podaci o starosti, polu, nivou formalnog obrazovanja, kao i o faktorima u vezi sa pušenjem prikupljeni su pomoću onlajn upitnika, dizajniranog za potrebe ovog skrininga. **Rezultati.** U istraživanju je učestvovalo 2.460 ispitanika (58,9% ženskog pola), prosečne starosti 63,7 ± 6,8 godina. Većina ispitanika bili su pušači (83,3%). Ukupno 48,7% je razmatralo mogućnost prestanka pušenja u prethodnih šest meseci, a u narednih mesec dana 24% nameravalo je da prestane sa pušenjem. Pacijenti koji su često ili vrlo često bili zabrinuti zbog rizika od karcinoma pluća bili su spremniji da ostave cigarete u odnosu na one koji to nisu (33,3% prema 16,2%), p < 0,001. **Zaključak.** Utvrđen je nizak stepen lične odluke ispitanika za prestanak pušenja, kao i nedovoljno razvijena svest o riziku za nastanak karcinoma pluća. Pilot projekat za skrining karcinoma pluća trebalo bi proširiti na područje cele države, a lekari primarne zdravstvene zaštite treba da imaju aktivniju ulogu u odvikavanju od pušenja kod svih osoba.

Ključne reči: tumori pluća; primarna zdravstvena zaštita; pušenje; navike; skrining; demografija; znanje o zdravlju, stavovi, praksa

Introduction

Lung cancer (LC) ranks among the most prevalent neoplasms globally, with 2 million cases reported annually worldwide, leading to 1.7 million deaths [1, 2]. Smoking cessation is commonly integrated into international and national initiatives aimed at preventing malignant diseases due to the strong correlation between LC and smoking. Tobacco control is recognized as a significant measure in LC prevention. Various screening programs have been devised to target adults of varying ages, regardless of their smoking status, primarily focusing on individuals at heightened risk for LC development. The objective is to enable early detection and prompt initiation of treatment, thereby mitigating mortality [3−10]. The European action plan to combat cancer sets the target of reducing tobacco use in the general population to under 5% by 2040 [11, 12]. Low-dose computed tomography (LDCT) has been

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Abbreviations

LC – lung cancer
LDCT – low-dose computed tomography
PY – pack-years
CT – computed tomography
BMI – body mass index

utilized in LC screening worldwide for decades, with the aim of achieving the same goal [2, 13–16].

According to the Serbian Cancer Registry of the Institute of Public Health of Serbia, "Dr. Milan Jovanovic Batut", there were 6,863 new LC cases (2,069 in women and 4,794 in men) registered in 2019, making it the second most common cancer among women (10.5%) and the most common cancer among men (21.3%) in Serbia [17, 18]. These concerning statistics were confirmed by an observational study based on hospital registry data from the Institute for Pulmonary Diseases of Vojvodina for the period spanning 2011 to 2020. The number of diagnosed lung cancers in Vojvodina had increased compared to the preceding decade, with a significantly higher incidence in females [19]. In an effort to reverse these trends, LC screening using LDCT was launched at the Institute for Pulmonary Diseases of Vojvodina in September 2020. The Primary Healthcare Center Novi Sad was included in the selection of subjects for the screening program, and the results obtained thus far have been published in several papers [20, 21].

Daily interaction with patients plays a very important role in motivating them to quit smoking and sustaining abstinence. The objective of this study was to analyze smoking-related habits among participants in the LC screening program.

Material and Methods

The cross-sectional study was conducted from September 29, 2020 to June 9, 2023. Relevant database records containing information on the socio-demographic characteristics of patients treated at the Primary Healthcare Center Novi Sad were analyzed. The research was approved by the Ethics Committee of the Primary Healthcare Center Novi Sad (Decision number: 21/32-1) as a part of the pilot project titled "Early Detection of Lung Cancer".

During the observed period, records of 2,460 participants were included in the database. Written informed consent was provided to all participants by their designated physicians during regular health visits, with a compliance rate of 100%.

Socio-demographic characteristics (age, gender, level of formal education) and smoking-related habits were assessed using an electronic questionnaire specifically designed for the project.

Only individuals meeting the following inclusion criteria were eligible for participation: (1) age between 50 and 74 years, active smoker with a smoking history of ≥30 years, consuming one or more packs per day (equivalent to 30 pack-years (PY) calculated by dividing the number of cigarettes smoked per day by 20 and multiplying the result by the number of years of smoking [22]); or (2) age between 50 and 74 years, active smoker with a smoking history of ≥ 20 years, consuming one or more packs per day (equivalent to 20 PY), and having one or more associated risk factors: chronic lung disease, previous cancer diagnosis (established more than five years ago and no longer under follow-up), family history of lung cancer, or occupational exposure to carcinogenic substances; or (3) age between 50 and 74 years, former smoker who quit smoking 1 to 10 years prior to the screening, with the same risk factors as active smokers mentioned above, but without the symptoms or signs of lung cancer.

The final sample was formed by applying the following exclusion criteria: age below 50 or above 74; cessation of smoking for more than 10 years; regular lung CT findings within the past 12 months; previous lung cancer diagnosis (as these individuals are covered by a special monitoring system); continuous use of a home oxygen concentrator; presence of other comorbidities in an advanced stage, such as advanced liver disease, chronic obstructive pulmonary disease (COPD) with hypoventilation and hypoxia, or congestive heart failure (New York Hearth Association stage IV), where the expected length of survival due to the underlying disease limits the potential benefits of screening.

Differences between categorical variables were assessed using the Chi-squared test, while one-way ANOVA was employed to test differences between groups. Quantitative parameters were described as Mean (M) ± Standard Deviation (SD), while percentages and frequencies were reported for qualitative parameters. A probability level of $p \leq 0.05$ was considered statistically significant. All statistical analyses were conducted using the SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Out of 2,460 respondents, 41.1% were males and 58.9% females. The average age of the respondents was 63.7±6.8 years. The average body mass of the respondents was 78.0±17.6 kg, with an average height of 169.3±9.8 cm. Among the participants, 44 (1.8%) were undernourished, 863 (35.2%) had normal weight, 1002 (40.8%) had increased body mass, and 546 (22.2%) were obese. The majority of the participants had a spouse or a cohabiting partner (1579 or 64.2%), 132 (5.4%) were single, 340 (13.8%) were divorced, and 409 (16.6%) were widows/widowers. In terms of educational level, 227 (9.2%) had completed primary school, 1673 (68.0%) had completed secondary school, 231 (9.4%) had higher education, and 306 (12.4%) participants had a university degree. Other forms of education were reported by 23 (0.9%) participants. In terms of employment status, 932 (37.9%) were employed, 310 (12.6%) were unemployed, 1188 (48.3%) were retirees, 30 (1.2%) were part time workers, and 30 (1.2%) were early retirees due to medical conditions. Over the last 20 years, 473 (19.2%) participants reported changing their place of residence, while remaining 1987 (80.8%) did not **(Table 1).**

Table 1. Sociodemographic characteristics of the participants
Tabela 1. *Socio-demografske karakteristike ispitanika*

Sex/*Pol*	N (%)/*Br. (%)*
Male/*Muški*	1,011 (41.1%)
Female/*Ženski*	1,449 (58.9%)
Age (years), M±SD (range)/*Starost (godine), M±SD (raspon)*	63.7±6.8
Body mass (kg), M±SD (range)/*Telesna masa (kg), M±SD (raspon)*	78.0±17.6 (37.0−191.0)
Height (cm), M±SD (range)/*Visina (cm), M±SD (raspon)*	169.3±9.8 (120.0−202.0)
BMI (kg/m^2) M±SD (range)/*Indeks telesne mase (kg/m^2), M±SD (raspon)*	27.1±5.2 (13.5−65.8)
BMI categories/*BMI kategorije*	N (%)/*Br. (%)*
≤ 18.5 (Underweight/*Pothranjenost*)	44 (1.8%)
18.5−24.9 (Healthy weight/*Normalna telesna masa*)	863 (35.2%)
25.0−29.9 (Overweight/*Povećana telesna masa*)	1,002 (40.8%)
≥ 30 (Obesity/*Gojaznost*)	546 (22.2%)
Marital status/*Bračni status*	N (%)/*Br. (%)*
Living with a partner (marital/extramarital)/*Život u zajednici (bračni/vanbračni)*	1,579 (64.2%)
Single/*Neoženjen/neudata*	132 (5.4%)
Divorced/*Razveden/razvedena*	340 (13.8%)
Widowed/*Udovac/udovica*	409 (16.6%)
Educational attainment/*Nivo formalnog obrazovanja*	N (%)/*Br. (%)*
Primary school/*Osnovna škola*	227 (9.2%)
Secondary school/*Srednja škola*	1,673 (68.0%)
Post-secondary vocational education/*Viša škola*	231 (9.4%)
University/*Fakultet*	306 (12.4%)
Other/*Ostalo*	23 (0.9%)
Current employment status/*Trenutni radni status*	N (%)/*Br. (%)*
Employed/*Zaposlen*	932 (37.9%)
Unemployed/*Nezaposlen*	310 (12.6%)
Retired/*Penzioner*	1,188 (48.3%)
Retired prematurely due to illness/*Prevremeno penzionisan zbog bolesti*	30 (1.2%)
Change of residence in the last 20 years/*Promena mesta boravka u poslednjih 20 godina*	N (%)/*Br. (%)*
Yes/*Da*	473 (19.2%)
No/*Ne*	1,987 (80.8%)

Legend*:* N – number of participants; M – mean; SD – standard deviation; BMI – body mass index
Legenda: Br. – broj ispitanika; M – srednja vrednost; SD – standardna devijacija; BMI – indeks telesne mase

As shown in **Table 2**, during the 12 months preceding the survey, 351 (14.3%) participants underwent a chest X-ray, averaging 1.3±0.8 chest X-rays per participant, 32 (1.3%) had lung CT scan, averaging 1.2±0.8 CT scans per participant, and 138 (5.6%) underwent mammography. The average tobacco smoke exposure among participants was 21.8±12.4 years. Regarding tobacco smoking status, 2048 (83.3%) were smokers, 402 (16.3%) were ex-smokers, and 10 (0.4%) were non-smokers. The average number of years of smoking was 36.7±9.0 years, with an average number of cigarettes smoked per day of 22.0±7.9. The average PY value was 40.1±17.4 years. Among ex-smokers, the average number of years since smoking cessation was 7.6±7.0 years. Among the 2435 participants who reported the type of cigarettes smoked, 1986 (81.6%) smoked commercial cigarettes, 428 (17.5%) smoked hand-rolled cigarettes, 19 (0.8%) used e-cigarettes, and 2 (0.1%) smoked pipes. Regarding the option of quitting smoking in the previous 6 months, 962 (48.7%) out of 1977 participants considered quitting, while 1015 (51.3%) did not. Regarding the intention to quit smoking in the next 30 days, 477 (24.0%) out of 1984 participants were affirmative about it. In terms of exposure to tobacco smoke during childhood/teenage years, 999 (40.6%) reported no exposure, 311 (12.7%) reported occasional exposure, 524 (21.3%) reported moderate exposure, and 626 (25.4%) reported frequent exposure. Regarding exposure to tobacco smoke during adulthood at work or at home 396 (16.1%) reported no exposure, 242 (9.9%) reported occasional exposure, 653 (26.5%) reported moderate exposure, and 1169 (47.5%) participants reported frequent exposure. Concerning the likelihood of developing lung cancer, 651 (26.5%) participants never worried, 362 (14.8%) rarely worried, 953 (38.7%) occasionally worried, 360 (14.6%) frequently worried, and 134 (5.4%) very frequently worried **(Table 2).**

Table 2. Smoking practices, habits and attitudes of the participants
Tabela 2. *Praksa, navike i stavovi ispitanika o pušenju cigareta*

Did you have a chest X-ray in the last 12 months?/*Da li ste u poslednjih 12 meseci imali rendgenski pregled pluća,* N/*Br. (%)*	
Yes/*Da*	351 (14.3%)
No/*Ne*	2109 (85.7%)
How many chest X-rays did you have in the last 12 months? M±SD (range) *Koliko ste rendgenskih pregleda pluća imali u poslednjih 12 meseci? M±SD (raspon)*	1.3±0.8 (1.0−8.0)
Did you have a chest CT in the last 12 months?/*Da li ste u poslednjih 12 meseci imali kompjutersku tomografiju pluća?*	
Yes/Da	32 (1.3%)
No/*Ne*	2428 (98.7%)
How many times did you have chest CT in the last 12 months? M±SD (range) *Koliko puta ste u poslednjih 12 meseci imali kompjutersku tomografiju pluća? M±SD (raspon)*	1.2±0.8 (1.0−5.0)
Did you undergo mammography in the last 12 months?/*Da li ste imali mamografiju u poslednjih 12 meseci?* N/*Br. (%)*	
Yes/*Da*	138 (5.6%)
No/*Ne*	2,322 (94.4%)
How long have you been exposed to tobacco smoke for? years, M±SD (range) *Koliko dugo ste bili izloženi duvanskom dimu? godine, M±SD (raspon)*	21.8±12.4 (1.0−50.0)
Smoking status/*Pušački status*	N/*Br.* (%)
Smoker/*Pušač*	2048 (83.3%)
Ex-smoker/*Bivši pušač*	402 (16.3%)
Nonsmoker/*Nepušač*	10 (0.4%)
How many years have you been smoking/did you smoke daily? M±SD (range) *Koliko godina redovno (svakodnevno) pušite ili ste pušili? M±SD (raspon)*	36.7±9.0 (1.0−65.0)
How many cigarettes do/did you consume daily? M±SD (range) *Koliko ste u proseku pušili/pušite cigareta, M±SD (raspon)*	22.0±7.9 (1.0−80.0)
Pack-years (PY), M±SD (range)/*Paklo – godina (PG), M±SD* (*raspon*)	40.1±17.4(1.0−174.0)
If you are an ex-smoker, how many years ago did you quit? M±SD (range) *Ako ne pušite, koliko godina ima od kada ste prestali da pušite? M±SD (raspon)*	7.6±7.0 (1.0−55.0)
Type of cigarettes you most often consume/consumed/*Vrsta cigarete koje najčešće pušite/ste pušili?*	N/*Br.* (%)
Commercial cigarettes/*Cigarete - fabričke*	1,986 (81.6%)
Hand-rolled cigarettes/Cigarete - *Sopstvene izrade*	428 (17.5%)
E-cigarettes/*E-cigarete*	19 (0.8%)
Pipe/*Lula*	2 (0.1%)
Have your considered quitting smoking in the past 6 months? (N=1977) *Da li ste razmotrili mogućnost prestanka pušenja u prethodnih 6 meseci? (Br.=1977)*	N/*Br.* (%)
Yes/*Da*	962 (48.7%)
No/*Ne*	1,015 (51.3%)
Do you plan to quit smoking in the next 30 days?/*Da li planirate da prestanete pušiti u narednih 30 dana?* N/*Br.*=1984*)*	
Yes/*Da*	477 (24.0%)
No/*Ne*	1,507 (76.0%)
Were you exposed to tobacco smoke as a child or teenager (<18 years)? *Da li ste kao dete i tinejdžer (< 18 godina) bili izloženi duvanskom dimu?*	N/*Br.* (%)
No/*Ne*	999 (40.6%)
Occasionally/*Vrlo malo*	311 (12.7%)
Moderately/*Umereno*	524 (21.3%)
Frequently/*Često*	626 (25.4%)
Were you exposed to tobacco smoke at home or workplace as an adult? *Da li ste kao odrasli bili izloženi duvanskom dimu kod kuće/radnom mestu?*	N/*Br.* (%)
No/*Ne*	396 (16.1%)
Occasionally/*Vrlo malo*	242 (9.9%)
Moderately/*Umereno*	653 (26.5%)
Frequently/*Često*	1,169 (47.5%)
How often do you worry about your lung cancer risk? *Koliko često ste zabrinuti zbog sopstvenog rizika za nastanak karcinoma pluća?*	N/*Br.* (%)
I am not worried/*Nisam zabrinut/zabrinuta*	651 (26.5%)
Rarely/*Retko*	362 (14.8%)
Occasionally/*Ponekad*	953 (38.7%)
Frequently/*Često*	360 (14.6%)
Very frequently/*Vrlo često*	134 (5.4%)

Legend*:* N – number of participants; M (mean) ±SD (standard deviation)
*Legenda***:** *Br. – broj ispitanika; M (srednja vrednost) ±SD (standardna devijacija)*

Table 3. Practices, habits and attitudes of participants related to willingness to quit smoking
Tabela 3. *Praksa, navike i stavovi ispitanika u odnosu na spremnost da prestanu s pušenjem cigareta*

	Willing to quit smoking *Planiranje prekida aktivnog pušačkog statusa*		p/*p*
	Yes/*Da*	No/*Ne*	
Did you have a chest X-ray in the last 12 months?/*Da li ste u poslednjih 12 meseci imali rendgenski pregled grudnog koša?*			< 0.001
Yes/*Da*	90 (18.9%)	181 (12%)	
No/*Ne*	387 (81.1%)	1,326 (88%)	
Total/*Ukupno*	477	1,507	
Did you have a chest CT in the last 12 months? *Da li ste u poslednjih 12 meseci imali kompjutersku tomografiju grudnog koša?*			0.008
Yes/*Da*	12 (2.5%)	14 (0.9%)	
No/*Ne*	465 (97.5%)	1,493 (99.1%)	
Type of cigarettes you most often consume/consumed?/*Vrsta cigarete koje najčešće pušite ili ste pušili?*			0.001
Commercial cigarettes/*Cigarete – fabričke*	398 (83.6%)	1,163 (77.3%)	
Hand-rolled cigarettes/*Cigarete – Sopstvene izrade*	70 (14.7%)	329 (21.9%)	
E-cigarettes/*E-cigarete*	8 (1.7%)	10 (0.7%)	
Pipe/*Lula*	0 (0%)	2 (0.1%)	
Total/*Ukupno*	476	1,504	
How often do you worry about your risk of developing lung cancer? *Koliko često ste zabrinuti zbog sopstvenog rizika za nastanak raka pluća?*			< 0.001
I am not worried/*Nisam zabrinut/zabrinuta*	80 (16.8%)	430 (28.5%)	
Rarely/*Retko*	55 (11.5%)	230 (15.3%)	
Occasionally/*Povremeno*	183 (38.4%)	603 (40%)	
Frequently/*Često*	113 (23.7%)	179 (11.9%)	
Very frequently/*Vrlo često*	46 (9.6%)	65 (4.3%)	
Total/*Ukupno*	477	1,507	

Legend*:* N – number of participants; p value – level of statistical significance/*Legenda: Br. – broj ispitanika; p – nivo statističke značajnosti*

Table 4. Correlation between smoking history and exposure to tobacco smoke
Tabela 4. *Povezanost dužine pušačkog staža sa izloženošću duvanskom dimu*

	Smoking history (years) *Dužina pušačkog staža (godine)* (M±SD)	p/*p*
Were you exposed to tobacco smoke as a child or teenager (<18 years)? *Da li ste kao dete i tinejdžer (< 18 godina) bili izloženi duvanskom dimu?*	N (%)/*Br. (%)*	0.007
No/*Ne*	36.0 ±9.0	
Occasionally/*Povremeno*	36.9 ±8.2	
Moderately/*Umereno*	36.6±9.2	
Frequently/*Često*	37.6±9.2	
Were you exposed to tobacco smoke at home or workplace as an adult? *Da li ste kao odrasli bili izloženi duvanskom dimu kod kuće ili radnom mestu?*	N (%)/*Br. (%)*	< 0.001
No/*Ne*	35.2±8.7	
Occasionally/*Povremeno*	36.3±8.3	
Moderately/*Umereno*	36.2±9.4	
Frequently/*Često*	37.5±8.9	
Current employment status/*Trenutni radni status*	N (%)/*Br. (%)*	< 0.001
Employed, zaposlen/*Zaposlena*	33.5±7.1	
Unemployed, nezaposlen/*Nezaposlena*	35.3±7.8	
Retired, penzioner/*Penzionerka*	39.6±9.7	
Retired prematurely due to illness/*Prevremeno penzionisan/penzionisana zbog bolesti*	36.0 ±.12	

Legend*:* N – number of participants; M – mean; SD – standard deviation; p value – level of statistical significance
Legenda: Br. – broj ispitanika; M – srednja vrednost; SD – standardna devijacija; p – nivo statističke značajnosti

Table 3 presents an analysis of a subset consisting of 477 participants who reported intending to quit smoking within the next 30 days. Of these patients, 90 (18.9%) had undergone a chest X-ray in the previous 12 months, while 12 (2.5%) had a chest CT scan. Out of 476 participants who provided information about the type of cigarettes they smoked, 398 (83.6%) smoked commercial cigarettes, 70 (14.7%) smoke hand-rolled cigarettes, 8 (1.7%) used e-cigarettes and none reported smoking a pipe. All participants answered the question about their concern regarding the possibility of developing lung cancer with the following distribution: 80 (16.8%) never worried, 50 (11.5%) rarely worried, 183 (38.4%) occasionally worried, 113 (23.7%) frequently worried and 46 (9.6%) very frequently worried.

Among 1507 participants who reported not planning to quit smoking in the next 30 days, 181 (12%) had undergone a chest X-ray in the previous 12 months, while 14 (0.9%) had a chest CT scan. Out of 1504 who provided information about the type of cigarettes they smoked, 1163 (77.3%) smoked commercial cigarettes, 329 (21.9%) smoked hand-rolled cigarettes, 810 (0.7%) used e-cigarettes, and 2 (0.1%) smoked pipes. All participants answered the question about their concern regarding the possibility of developing lung cancer with 430 (28.5%) reporting never being worried, 230 (15.3%) rarely being worried, 603 (40%) occasionally being worried, 179 (11.9%) frequently being worried, and 65 (4.3%) very frequently being worried.

The results indicate that participants who were not exposed to tobacco smoke during childhood or as teenagers had the shortest duration of smoking in years (36.0 ±9.0), while those frequently exposed had the longest duration (37.6±9.2, p=0.007). Similarly, participants who were frequently exposed as adults had the longest duration of smoking in years (37.5±8.9), while those not exposed had the shortest (35.2±8.7, p<0.001). Employed participants had the shortest duration of cigarette consumption (33.5±7.1), while retirees consumed cigarettes for the longest period of time (39.6±9.7, p<0.001) **(Table 4).**

Discussion

Although the risks of smoking to human health are well known, tobacco consumption remains the leading preventable cause of death and illness across all age groups, regardless of sex and geographic location [23]. However, it is noteworthy that the present study focused on adults aged 50 or above. Hence, it is valuable to compare our findings with those of a study conducted in 12 European states, which included a much broader age range [24]. The authors observed that educational differences between smokers and nonsmokers were more pronounced in the 20−44 age group, where less educated individuals were more likely to be smokers in most countries. In the 45−74 age group, directly comparable to our cohort, a correlation between active/former smoker status and lower educational attainment was noted in only a few countries [24]. Empirical evidence also suggests that smokers living in a nonsmoking household are more likely to quit compared to those living alone or with a partner who smokes. Particularly, having a partner who is an ex-smoker increases the likelihood of quitting by 5-fold relative to being single [25]. These findings are expected, as cohabiting couples frequently share lifestyle habits. Therefore, healthcare professionals should involve partners of smokers in activities aimed at smoking cessation [23].

As our research was conducted as part of an LDCT screening pilot project, the study sample predominantly consisted of smokers (83.3%), who reported a smoking history. This sample composition aligns with prevailing international guidelines on LDCT screening, which target active or ex-smokers (those who stopped smoking within the last 15 years), with a smoking history of 25–30 PY and aged 50/55–75/80 years [26, 27]. The significance of such initiatives is highlighted by findings reported by Antonic D et al., indicating that in the Republic of Srpska, about 70% of newly diagnosed lung and trachea cancer cases and resulting deaths occurred in the 50−74 age group. The largest number of active smokers was noted in the 35−44 age group, with an average smoking history of about 20 years. Lung and trachea cancer were more common among men, who were also more likely than women to be active smokers [28]. Ex-smokers who participated in our study quit an average of 7.6±7.0 years ago, while 48.7% of active smokers considered the possibility of quitting smoking in the last six months. Although most smokers recognize the highly harmful nature of tobacco consumption, their willingness to quit smoking is associated with their motivation to change bad habits and improve their health, as well as other factors [29]. Motivation to quit smoking and addiction to cigarettes are interrelated, and empirical evidence indicates that motivation to stop smoking can vary over time and is often influenced by the smoker's immediate environment [30]. Blondé J et al. found that the level of self-affirmation was positively related to higher motivation to quit among smokers in the high-dependency group but not among those exhibiting low-dependency traits [31]. However, identifying the factors that influence smoking cessation success rates is challenging due to considerable differences in results reported in the relevant literature. For example, Granda-Orive JI et al. surveyed 273 adults, of whom 147 or 53.8% were women, with an average age of 51±11 years. They found that within 12 months, 53.5% of subjects (36.13% according to the intention-to-treat analysis) (n=146, 66 men and 80 women) quit smoking, with no statistically significant differences between sexes [32]. In another study involving 759 smokers, 32.4% reported not having smoked for at least 30 days at the 6-month follow-up. Additionally, 72.5% of participants attempted to quit smoking at least once, while 12.5% made at least three attempts. The authors observed that smoking cessation success was significantly predicted by older age at smoking initiation, non-

exposure to secondhand cigarette smoke, fewer quitting attempts, lower cigarette consumption, use of tobacco gum or patches, and lower carbon monoxide concentration at baseline [33]. With recent technological advances, smokers now have access to a wide range of mobile applications to support smoking cessation, particularly beneficial for those ambivalent about quitting and constantly delaying the decision [34, 35]. Further research is required to assess whether mobile applications can complement or replace traditional smoking cessation approaches [34].

Antuleska Belceska G et al. found a statistically significant association between professional exposure to tobacco smoke (16.2%) and positive family history of LC (20.8%) with lung cancer among their 173 study participants [36]. In our research, 14.6% and 5.4% of respondents respectively indicated that they are often and very often concerned about their lung cancer risk. Interestingly, those who had a chest X-ray or CT scan in the preceding 12 months were more willing to quit smoking, which could also be interpreted as an increased concern for their health. In a study conducted in Poland involving 618 subjects (385 of whom were ex-smokers), 77% of respondents attempted to quit smoking on their own. They stated general concern for health (57%), personal health problems (32%), and social reasons (32%) as the primary motivators [37].

Conclusion

We have identified a low level of personal decisions to quit smoking, along with a concerning lack of awareness regarding the risks of developing lung cancer.

Physicians working in the primary healthcare settings should take a more proactive role in smoking cessation initiatives. Additional support at the primary healthcare level should be extended to individuals who have quit smoking, aimed to reinforce their decision by implementing preventive and corrective measures.

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PREVALENCE OF VAGINAL INFECTIONS AND COMPLIANCE OF EMPIRICALLY PRESCRIBED THERAPY WITH THE RESULTS OF VAGINAL SWABS IN THE FEMALE POPULATION AT THE LEVEL OF PRIMARY HEALTH CARE

PREVALENCIJA VAGINALNIH INFEKCIJA I USKLAĐENOST EMPIRIJSKE TERAPIJE SA REZULTATIMA VAGINALNIH BRISEVA U POPULACIJI ŽENA NA NIVOU PRIMARNE ZDRAVSTVENE ZAŠTITE

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Summary

Introduction. Vaginal infections are the most common reason for gynecological exams. Due to the absence of national guidelines on screening and treatment, therapy is prescribed empirically. The aim of this study is to determine (1) the prevalence of vaginal infections in community practice setting, (2) infection prevalence across different groups, and (3) appropriateness of empirical therapy. **Material and Methods.** Results from 1770 vaginal swabs collected between June 2021 and June 2023 were classified into three groups: group 1 – young adult women (≤ 25 years), group 2 – women of reproductive age (26-45 years), group 3 – peri- and postmenopausal women (≥46 years). The study analyzed the population prevalence of vaginal infections, including bacterial vaginosis, vulvovaginal candidiasis, and pathogenic bacterial groups, as well as the appropriateness of the prescribed empirical therapy. **Results**. The prevalence of vaginal infection was 41.07%, with 24.07% of the population exhibiting symptomatic infections, and the remaining 17% having positive swab results subsequently. The population prevalence of bacterial vaginosis, vulvovaginal candidiasis, and pathogenic bacteria was 41.95%, 35.62% and 22.42%, respectively. The highest prevalence was observed in group 1, followed by group 3, and the lowest in group 2 (51.02%, 42.6%, 38.7%, respectively, p=0.175). The prevalence of bacterial vaginosis and vulvovaginal candidiasis in group 1 was 54.95%/45.04%, in group 2 was 53%/46.93%, and in group 3 was 57.69%/42.3% (p=0.028). Pathogenic bacteria isolation was highest in group 3 (49.4%) and lowest in group 1 (21.79%). Correction of empirical therapy was required in 36.55% of symptomatic women. **Conclusion**. Bacterial vaginosis and vulvovaginal candidiasis exhibit similar prevalence rates in groups 1 and 2, while pathogenic bacteria infections are most common group 3. When choosing therapy, it is important to consider patient age in relation to other predisposing factors associated with vaginal infections. **287 reči**

Key words: Vaginal Diseases; Vaginosis, Bacterial; Candidiasis, Vulvovaginal; Vaginal Smears; Treatment Outcome

Sažetak

Uvod. Vaginalne infekcije najčešći su razlog ginekološkog pregleda. Ne postoje nacionalne smernice za skrining i lečenje, te se terapija ordinira empirijski. Cilj rada je utvrđivanje (1) prevalencije infekcije populacije u primarnoj zdravstvenoj zaštiti, (2) prevalencije infekcije u formiranim grupama, (3) adekvatnost empirijski prepisane terapije. **Materijal i metode.** Rezultati 1.770 vaginalnih briseva (jun 2021–jun 2023), razvrstani su u grupe: Grupa 1 − mlade odrasle žene (≤ 25 god), Grupa 2 − žene reproduktivnog perioda (26−45 god), Grupa 3 − žene u perimenopauzi i postmenopauzi (≥ 46 god). Analizirana je prevalencija vaginalne infekcije populacije, bakterijske vaginoze, vulvovaginalne kandidijaze i patogenih bakterija formiranih grupa, te prepisana empirijska terapija. **Rezultati**. Prevalencija vaginalne infekcije je 41,07%, od čega je u 24,07% populacije registrovana simptomatska infekcija, a u preostalih 17% vaginalni bris je naknadno došao pozitivan. Prevalencija bakterijske vaginoze, vulvovaginalne kandidijaze i patogenih bakterija populacije je 41,95%, 35,62% i 22,42%. Najveća prevalencija infekcije je u Grupi 1, potom Grupi 3 a najmanja u Grupi 2 (51,02%, 42,6%, 38,7% respektivno, p 0,175). Zastupljenost bakterijske vaginoze i kandidijaze u Grupi 1 je 54,95%/45,04%; Grupi 2 53%/46,93%; Grupi 3 57,69%/42,3% (p 0,028) dok je izolacija patogenih bakterija najveća u Grupi 3 (49,4%), a najmanja u Grupi 1 (21,79%). Korigovanje empirijski date terapije bilo je potrebno kod 36,55% žena sa simptomima. **Zaključak.** Prevalencija bakterijske vaginoze i vulvovaginalne kandidijaze podjednaka je u grupama 1 i 2, dok je infekcija patogenim bakterijama najčešća vaginalna infekcija u Grupi 3. Pri odabiru terapije treba razmotriti godine usled povezanosti sa predisponirajućim faktorima.

Ključne reči: vaginalne infekcije; bakterijske vaginoze; vulvovaginalna kandidijaza; vaginalni bris; ishod lečenja

Introduction

The primary complaint of women visiting gynecological offices is vaginal discharge [1, 2], with a

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Abbreviations
VI – vaginal infection
VS – vaginal swab
BV – bacterial vaginosis
VVC – vulvovaginal candidiasis

symptomatic vaginal infection (VI) incidence up to 50% [3]. Typically, in symptomatic patients, empirical therapy is prescribed based on clinical presentation (vaginal malodor, increased secretion, itching) and physical examination findings (appearance of vaginal secretions, mucous membrane erythema, odor, vaginal pH) to alleviate or eliminate symptoms until vaginal swab (VS) results are available [3]. Several predisposing factors contribute to acquiring VI, including sexual behavior history (number of partners), vaginal douching, contraceptive use, antibiotic use, race, education level, and menstrual cycle [3–5]. Based on these criteria, we stratified the population into age groups to determine the prevalence and incidence of VI within each group and identify the dominant infectious agents in these groups.

Material and Methods

This retrospective observational study analyzed VS results and prescribed therapies extracted from medical records of patients examined by four gynecologists at the Polyclinic "Novakov &Assoc." from June 2021 to June 2023. Included were cases where patients underwent examination and VS due to vaginal discharge syndrome, characterized by changes in amount or appearance of vaginal secretions, presence of itching and/or burning sensation, and appearance of unpleasant-smelling secretions. Additionally, cases where gynecological examinations were conducted for other indications (preventive examination, annual checkup, preparation for intervention/surgery) with vaginal secretions sampling were included. Data lacking information on swab results or prescribed therapy were excluded from analysis. A total of 1770 women were included and divided into three groups based on age and risk factors for vaginal infection: group 1 – young adult women (≤25 years) characterized by more frequent partner changes, contraceptive use, and self-medication; group 2 – women of reproductive age (26-45 years) characterized by monogamous relationships and cessation of contraception to achieve pregnancy; group 3 – perimenopausal/menopausal women (≥46 years) characterized by hormonal changes associated with declining estrogen levels leading to reduced glycogen in desquamated vaginal epithelial cells [6, 7]. Vaginal secretion samples were evaluated based on Nugent Gram stain score and cultivated for qualitative identification of specific organisms associated with bacterial vaginosis, pathogenic bacteria, and yeast.

Results

A total of 1770 women's medical records were analyzed from a primary women's healthcare setting. The average age of patients was 36 years, ranging from 17 to 86 years **(Table 1).** The prevalence of VI in the studied population was 41.07%, with

Table 1. Swab results according to specified patient groups
Tabela 1. *Rezultati briseva u formiranim grupama pacijentkinja*

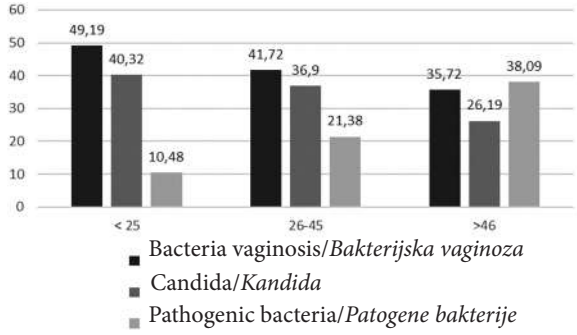
Swab result *Rezultat brisa*	Results distribution across specified patient groups *Distribucija nalaza u formiranim grupama*						Total *Ukupno*	
	Group 1/*Grupa 1*		Group 2/*Grupa 2*		Group 3/*Grupa 3*			
	N/*Br.*	%	N/*Br.*	%	N/*Br.*	%	N/*Br.*	%
Positive/*Pozitivan*	124	51.02	477	38.68	126	42.86	727	41.07
Negative/*Negativan*	119	48.97	756	61.31	168	57.14	1043	58.93
Total/*Ukupno*	243 (13.73%)		1233 (69.66%)		294 (16.61%)		1770	100%

Legend: group 1 – young adult women (≤25 years); group 2 – women of reproductive age (26-45 years); group 3 – perimenopausal/menopausal women (≥46 years)/*Legenda*: *grupa 1 – mlade odrasle žene (≤25 god); grupa 2 – žene reproduktivnog perioda (26-45 god); grupa 3 – žene u peri- i postmenopauzi (≥46 god)*

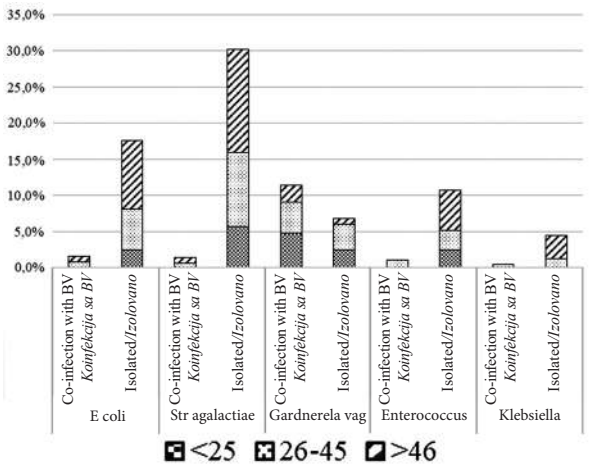
Table 2. Pathogen prevalence across age groups
Tabela 2. *Prevalencija uzročnika infekcija po starosnim grupama*

	Bacterial vaginosis *Bakterijska vaginoza*		Candida *Kandida*		Pathogenic bacteria *Patogene bakterije*		Total *Ukupno*
	N/*Br.*	%	N/*Br.*	%	N/*Br.*	%	N/*Br.*
Group 1/*Grupa 1*	61	49.19%	50	40.32%	17	10.48%	124
Group 2/*Grupa 2*	199	41.72%	176	36.9%	115	21.38%	477
Group 3/*Grupa 3*	45	35.72%	33	26.19%	44	38.09%	126
Total/*Ukupno*	305	41.95%	259	35.62%	163	22.42%	727

Legend: group 1 – young adult women (≤25 years); group 2 – women of reproductive age (26-45 years); group 3 – perimenopausal/menopausal women (≥46 years)/*Legenda*: *grupa 1 – mlade odrasle žene (≤25 god); grupa 2 – žene reproduktivnog perioda (26-45 god); grupa 3 – žene u peri- i postmenopauzi (≥46 god)*



Graph 1. Prevalence of infection pathogen across age groups
Grafikon 1*. Prevalencija uzročnika infekcija po starosnim grupama*



Graph 2. Distribution of pathogen agent across age groups
Grafikon 2. *Distribucija izolovanih patogenih uzročnika po grupama*

symptomatic VI occurring in 24.07% of cases. Bacterial vaginosis (41.95%) was the most common VI, followed by vulvovaginal candidiasis (35.62%) and isolated pathogenic bacterial flora (22.42%). Concurrent bacterial vaginosis (BV) with predominant pathogenic bacteria was observed in 14.75% of cases **(Table 2).** Among the age-stratified groups, IV prevalence was highest in young adult women (51.02%), followed by perimenopausal/menopausal women (42.86%), and lowest in women of the reproductive age (38.68%) (**Table 2**). The distribution of infectious agents within these groups showed equal prevalence of bacterial vaginosis and candidiasis in young adult women and women of the reproductive age (49.19% vs. 41.71% in group 1; 10.3% vs. 36.9% in group 2; p=0.028, **Graph 1**). In perimenopausal/menopausal women, a dominance of bacterial over candida VI was observed (57.69% vs. 42.3%, p=0.0712), with a decrease in nonspecific BV and an increase in isolated pathogenic bacterial infections (50.56% vs. 49.43%, p=0.107, **Table 3**), as demonstrated graphically in **Graph 2.** Empirical therapy was prescribed in 45.47% of cases during examination. Among confirmed infections (41.07% of cases),

Table 3. Distribution of isolated pathogen bacteria across the specified groups
Tabela 3. *Distribucija izolovanih patogenih bakterija po grupama*

		Group 1/*Grupa 1* (N/*Br.* = 124)	Group 2/*Grupa 2* (N/*Br.* = 477)	Group 3/*Grupa 3* (N/*Br.* = 126)	Total/*Ukupno* (N/*Br.* = 727)
E coli	Co-infection with BV *Koinfekcija sa BV*	0	4 (0.8%)	1 (0.8%)	5 (0.69%)
	Isolated/*Izolovano*	3 (2.4%)	27 (5.7%)	12 (9.5%)	42 (5.48%)
Streprococcus agalactiae	Co-infection with BV *Koinfekcija sa BV*	0	3 (0.6%)	1 (0.8%)	4 (0.55%)
	Isolated/*Izolovano*	7 (5.6%)	49 (10.3%)	18 (14.3%)	74 (10.18%)
Gardnerella vaginalis	Co-infection with BV *Koinfekcija sa BV*	6 (4.8%)	20 (4.2%)	3 (2.4%)	29 (3.99%)
	Isolated/*Izolovano*	3 (2.4%)	17 (3.6%)	1 (0.8%)	21 (2.89%)
Enterococcus	Co-infection with BV *Koinfekcija sa BV*	0	5 (1.0%)	0	5 (0.69%)
	Isolated/*Izolovano*	3 (2.4%)	13 (2.7%)	7 (5.6%)	23 (3.16%)
Klebsiella	Co-infection with BV *Koinfekcija sa BV*	0	2 (0.4%)	0	2 (0.27%)
	Isolated/*Izolovano*	0	6 (1.3%)	4 (3.2%)	10 (1.37%)

Legend: group 1 – young adult women (≤25 years); group 2 – women of reproductive age (26-45 years); group 3 – perimenopausal/menopausal women (≥46 years); BV – bacterial vaginiti/*Legenda: grupa 1 – mlade odrasle žene (≤25 god); grupa 2 – žene reproduktivnog perioda (26-45 god); grupa 3 – žene u peri- i postmenopauzi (≥46 god);* BV – bakterijski vaginitis

therapy required correction based on test results in 36.55% of cases, while therapy remained unchanged in 63.46% of cases. Notably, 5.4% of cases received therapy based on symptomatic presentation, despite negative vaginal sample results for infection.

Discussion

Vaginitis is a highly prevalent condition [5, 7–10] and represents the most common complaint among patients in women's healthcare settings [3, 11]. Discrepancies in guidelines [12–14], both internationally and due to the absence of national guidelines, contribute to significant variations in testing, treatment, and follow up recommendations. Currently, effective screening for BV is not routinely performed, suggesting a likely difference between actual and reported prevalence of BV [3]. The objective of this study was to investigate the prevalence of VI in general, unselected population, encompassing all women who visited out community practice setting during the study period. Published data BV prevalence range widely, from 20% to 60% [3, 8–10, 15], reflecting cultural factors [3] and variations among observed populations [8, 9, 15]. In our cohort, the frequency of symptomatic VI was 24.07%, while 17% of asymptomatic women who attended for routine or other gynecological reasons tested positive on smear tests, raising the prevalence to 41.07%. In essence, 4 out of 10 women undergoing gynecological examination were found to have some form of VI, whether symptomatic or asymptomatic. A noteworthy concern is the significant number of patients who self-diagnose and self-medicate, seeking professional consultation only after unsuccessful attempts to alleviate symptoms. This issue is particularly evident in vulvovaginal candidiasis (VVC), for which highly effective over-the-counter therapies are available, rapidly relieving the symptoms of uncomplicated infections, albeit without ensuring complete resolution [8, 10, 15]. For these reasons, it is quite certain that the incidence of VIs, including bacterial and vulvovaginal candidiasis VVC, is underestimated. The observed trend of IV incidence and prevalence being highest among young adult women aligns with the existing literature [2, 5, 6]. However, the notable increase in infections, particularly symptomatic cases, during the perimenopause/menopause phase is intriguing. Evidence underscores the significant impact of estrogen – specially its decline – in predisposing individuals to infection, highlighting the necessity to tailor therapy accordingly [6, 16]. The accuracy of empirically administered therapy is of paramount importance. Therefore, we analyzed the percentage of cases requiring therapy adjustment following receipt of vaginal swab (VS) results obtained during the visit, based on current treatment guidelines from the Center for Disease Control and Prevention (CDC) of the United States [12]. In 36.55% of cases, therapy correction was required, whereas in 63.46%, the therapy remained unchanged. It is important to note that medication was prescribed only in cases where symptoms or physical examination strongly indicated infection presence. A study conducted by the University of Pittsburgh on symptomatic vaginal infections found that therapy was prescribed in 34% of cases based on symptoms and a rapid on-site testing, despite subsequent negative smear results [8]. This "unnecessary" empirical therapy based on symptoms correlates with a higher rate of re-examination within 90 days compared to those not receiving therapy [8]. Our analysis revealed that in 5.4% of cases, therapy was prescribed due to suspected infection symptoms, yet the subsequent swab was negative. Furthermore, the issue of asymptomatic infections and the lack of treatment for transitional flora are crucial considerations. Using the Nugent score system a "gold standard" for diagnosing VIs to classify women in the intermediate group prompts the question of treatment necessity [8, 12, 17]. Given the high rate of vaginal infections (4 out of 10 women), the associated risks (such as increased susceptibility to human immunodeficiency virus, Neisseria gonorrhea, Chlamydia trachomatis, Trichomonas vaginalis, Herpes simplex virus type 2, pelvic inflammatory disease, intrauterine infection and premature birth [3, 6, 8, 10]), and relatively common inadequate treatment practices (self-medication, need for therapy correction in one third of cases), leads to the conclusion that addressing asymptomatic VIs or those classified in the intermediate group according to the Nugent score could mitigate the consequences of VI [3]. Recurrent BV may stem from reinfection (endogenous or from a partner) or relapse [3]. Dominant bacterial types (such as Atopobium vaginae, Gardnerella vaginalis), co-infection, and bacterial load are key factors contributing to bacterial vaginosis recurrence [10, 11, 18]. In the observed population, 14.75% of cases exhibited an intermediate or definitive BV (Nugent score ≥4) with dominance prevalence of pathogenic bacteria. Notably, specific pathogen isolation, with or without BV, defined as unspecific bacterial infection in test reports, was more pronounced among older patients (10.48% in young adult women vs. 38.09% in perimenopausal/menopausal women). This age-related trend likely stems from declining estrogen levels in this group [6, 16], supporting the assertion that age is a pivotal factor in empirically prescribing treatment.

Conclusion

The prevalence of unspecific bacterial infections, namely bacterial vaginosis and vulvovaginal candidiasis, is consistent across both the general population and in the defined age groups, with a notable increase in infection rates caused by isolated pathogenic bacteria among perimenopausal/menopausal women. When determining the appropriate therapy, in addition to considering the smear results, the patient's age should be taken into account due to its association with other predisposing factors.

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RISK FACTORS FOR PERITONEAL DISSEMINATION OF OVARIAN CANCER

FAKTORI RIZIKA ZA POJAVU PERITONEALNE DISEMINACIJE KARCINOMA JAJNIKA

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Summary

Introduction. Ovarian epithelial tumors constitute 60% of all ovarian tumors and approximately 90% of primary ovarian tumors. Most patients are diagnosed at an advanced stage of the disease. Epithelial ovarian tumors typically spread via transcoelomic dissemination, with about 70% of patients presenting with peritoneal metastases. Additionally, cancers can metastasize to the pelvic lymph nodes. The objective of this study was to identify which clinical characteristics of malignant ovarian cancer might influence the occurrence of peritoneal metastases. **Material and Methods.** This retrospective study involved histopathological analysis of 99 malignant ovarian tumors treated at the Institute of Oncology of Vojvodina between January 1, 2018 and December 31, 2020. The analysis included patient age, referral and final diagnosis, dimensions of ovaries, fallopian tubes, and tumor tissue, tumor bilaterality, histological type and grade, Tumor-Node-Metastasis classification, International Federation of Gynecology and Obstetrics stages of the tumor, ovarian capsule involvement, fallopian tube involvement, and presence of peritoneal implants. Patients were categorized into two groups: one with peritoneal dissemination of cancer and the other without peritoneal metastasis. **Results.** A statistically significant difference was observed between the presence of peritoneal dissemination and tumor bilaterality ($p \leq 0.05$), as well as capsular invasion by the primary tumor ($p \leq 0.05$). **Conclusion.** Specific clinical characteristics of ovarian cancer can aid in assessing the extent of primary ovarian tumor involvement and guide the selection of appropriate therapeutic interventions.

Key words: Ovarian Neoplasms; Carcinoma, Ovarian Epithelial; Risk Factors; Neoplasm Metastasis; Peritoneum

Sažetak

Uvod. Tumori epitela koji pokrivaju jajnike čine 60% svih tumora jajnika i oko 90% primarnih tumora jajnika. Većina pacijentkinja u trenutku postavljanja dijagnoze nalazi se u uznapredovalom stadijumu bolesti. Epitelni tumori jajnika se najčešće šire transcelomskim putem. Oko 70% pacijentkinja ima rezvijene peritonealne metastaze. Mnogi od ovih karcinoma imaju metastaze i u pelvičnim limfnim čvorovima. Cilj istraživanja bio je da se utvrdi koje kliničke karakteristike malignog tumora jajnika mogu uticati na pojavu peritonealnih metastaza ovarijalnog karcinoma. **Materijal i metode.** Studija je bila retrospektivna; obuhvatila je patohistološku analizu 99 malignih tumora jajnika, u periodu od 1. januara 2018. godine do 31. decembra 2020. godine, na Institutu za onkologiju Vojvodine. Analizirani su sledeći kliničko-demografski podaci: starost pacijentkinja, uputna i konačna dijagnoza, dimenzije jajnika, jajovoda i tumorskog tkiva, bilateralnost tumora, histološki tip i gradus tumora, klasifikacija: *Tumor*, *Čvor*, *Metastaze* i stadijumi tumora prema Međunarodnoj federaciji ginekologije i akušerstva, zahvatanje kapsule jajnika, zahvatanje jajovoda, prisustvo peritonealnih implanata. Pacijentkinje su podeljene u dve grupe. Prvu grupu su činile žene sa peritonealnom diseminacijom karcinoma, dok su drugu grupu činile žene bez peritonealnih metastaza. **Rezultati.** Postoji statistički značajna razlika ($p \leq 0,05$) između postojanja peritonealne diseminacije bolesti u odnosu na postojanje bilateralnosti malignog procesa, kao i u odnosu na kapsularnu invaziju primarnog tumora ($p \leq 0,05$). **Zaključak.** Odgovarajuće kliničke karakteristike ovarijalnog karcinoma mogu se koristiti u proceni proširenosti primarne ovarijalne tumorske promene, kao i u izboru adekvatnog terapijskog postupka.

Ključne reči: tumori jajnika; epitelni karcinom jajnika; faktori rizika; metastaze; peritoneum

Introduction

Ovarian epithelial tumors comprise of 60% of all ovarian tumors and around 90% of primary ovarian tumors [1, 2]. Malignant epithelial tumors are rare before the age of 40 and become more prevalent after menopause, similar to breast and endometrial tumors [1]. Ovarian cancer is the fifth leading cause of cancer-related deaths among women. In Serbia, approximately 820 cases of ovarian cancers are diagnosed each year [3].

The majority of patients are diagnosed with the disease at advanced stages, commonly in the third and fourth stages, due to the absence of early symptoms, leading to a poorer prognosis [2]. According to Juliette et al., 80% of patients present with advanced primary disease [4]. Despite therapeutic interventions, the five-year survival rate is 50%, indicating widespread disease in most patients. If metastases involve distant organs, even with surgical and chemotherapy treatments, the five-year survival rate decreases to 30% [5].

Ovarian epithelial tumors are heterogeneous in nature. Based on their origin, genetic characteristics,

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Abbreviations

TNM – Tumor, Node, Metastasis
FIGO – International Federation of Gynecology and Obstetrics
VEGF – vascular endothelial growth factor

and disease aggressiveness, tumors are classified into type I and type II. Type I tumors are genetically more stable, exhibiting slower growth and progression. Tumors in this category include low-grade serous carcinoma, endometrioid carcinoma, mucinous carcinoma, Brenner carcinoma, and clear cell carcinoma. In contracts, type II tumors demonstrate more aggressive behavior and higher mortality rates. Tumors in this group include high-grade serous carcinoma, carcinosarcoma, and undifferentiated carcinoma [6].

The ovarian surface epithelium shares the same embryonic origin as the coelomic mesothelium. Ovarian epithelial tumors typically spread via transcoelomic dissemination. About 70% of patients develop peritoneal metastasis, often involving omental metastasis assessed during diagnostic laparotomy to evaluate disease extent. Many of these cancers also exhibit metastasis in pelvic lymph nodes, highlighting a strong association between peritoneal and nodal metastasis [2, 7].

There are two hypotheses regarding the mechanism of peritoneal dissemination in primary ovarian disease. The first model, often referred to as the "seed and soil" hypothesis, suggests that tumors as genetically heterogeneous, and metastases originate from clones that have acquired a metastatic phenotype [8]. The genotype of the clone determines the tissue in which the cells will metastasize. According to the other theory, metastasis is a stochastic event, suggesting a small but real possibility that tumor cells will metastasize, and all tumor cells are homogeneous [9].

The process of metastasis in malignant ovarian carcinoma involves several key steps. Firstly, malignant cells must evade anoikis, a process in which cells undergo apoptosis when they lose contact with the extracellular matrix [10]. An important event in the development of metastatic potential is epithelial-mesenchymal transition, during which epithelial cells depolarize, intracellular connections are disrupted, and cells acquire morphological characteristics of fibroblasts, enabling adaptive migratory potential [2, 11]. This transition leads to the overexpression of endothelin 1 and its receptors, and reduced expression of E-cadherin [12].

Further evidence enhancing our understanding of adaptive metastasis involves the existence of spheroids, which represent aggregated malignant cells in malignant ascites [13]. In in vitro studies have shown that spheroids exhibit greater resistance to the component complement system, as antibodies and component complements struggle to penetrate cell clusters [14].

Peritoneal metastasis can manifest as either microscopic or macroscopic. It has been established that complete surgical removal of macroscopic peritoneal implants significantly prolongs overall survival and disease-free survival [15]. Amate et al. reported that peritoneum is the most common site of recurrence following treatment for ovarian malignancy [16]. When considering micrometastases, Schroff et al. identified their presence in 5% of cases on seemingly healthy peritoneum. The five-year survival for patients with micrometastases was 61.83% compared to 88.25% for patients without occult dissemination [17, 18].

This study was prompted by the high incidence of ovarian cancer among female patients and the presence of peritoneal metastasis at the time of diagnosis. Our aim was to investigate which clinical characteristic of malignant ovarian tumors influence the occurrence of peritoneal metastasis.

Material and Methods

The research was conducted retrospectively, involving the histopathological examination of 99 malignant ovarian tumors from January 1, 2018, to December 31, 2020, at the Oncology Institute of Vojvodina, following ovarian and fallopian tube surgeries. The histopathological analysis adhered to the protocol outlined by the College of American Pathologists (CAP) in 2018.

The methods used during the histopathological analysis of the ovarian tumors included:

1. Macroscopic analysis including the description of the received resected one or both ovaries with or without the fallopian tubes, uterus, lymph nodes and peritoneum; measurement of dimensions of ovaries, fallopian tubes, and tumor tissue (cm); description of the appearance of tumor tissue (shape, size, and color), localization, and edges (limits, presence of the tumor capsule, invasive growth, infiltration of ovarian capsule, fallopian tubes, uterus, or surrounding peritoneum); serial cutting of resected material perpendicularly along the longest axis into 3 mm thick slices.
2. Tissues were fixed in 10% neutral formalin, dehydrated in increasing concentrations of ethanol (70%, 80%, 96%, 100%), embedded in paraffin, and cut into 4 μm thick sections using a rotary microtome (Leica). All sections were stained with hematoxylin-eosin.
3. Microscopic histopathology examination was performed by pathologist using a light microscope to determine a definitive histopathological diagnosis based on histomorphological characteristics of tumor tissue.

All patients with complete medical history, including present symptoms, comorbidities, family history, allergies, and chronic therapies (if any), were included in this study. Additionally, each patient needed to have a noted final histopathological diagnosis and indication of peritoneal dissemination of carcinoma. Patients with incomplete medical histories and verified benign tumor masses were excluded from this research. After conducting macroscopic and microscopic analysis of the tissue samples obtained, the following data was analyzed: age of the patient, referral and final diagnosis, dimensions of the ovaries, fallopian tubes, and tumor tissue, bilaterality of the tumor, histologic type and grade, according to the tumor-node-metastasis (TNM) (AJCC 8th Edition) and the International Federation of Gynecology and Obstetrics (FIGO) tumor stages, ovary capsule involvement, fallopian tubes involvement, presence of peritoneal implants.

Patients with histopathologically confirmed ovarian cancer were divided into two groups based on the presence or absence of peritoneal dissemination of ovarian carcinoma. We recorded the number of patients younger than 50 years and those older than 50 years of age. Descriptive statistics were employed to ascertain the mean age of patients, distribution of carcinoma grade, disease stage, bilaterality, ovarian capsule invasion, uterine tubal involvement, and the utilization of neoadjuvant therapy. To investigate the relationship between the existence of peritoneal dissemination and patient age, we used a T-test to determine statistical significance. Chi square (χ^2) tests were used to assess whether there was a statistically significant association between peritoneal dissemination of the primary tumor and malignancy grade, disease stage, bilaterality, ovarian capsule invasion, and fallopian tube involvement. Differences in the number of removed lymph nodes and lymph nodes with metastatic deposits between groups with and without peritoneal dissemination were analyzed using the Mann-Whitney U test. The staging of ovarian tumors was determined according to the TNM classification [19] and FIGO criteria [20].

Results

The mean age of patients was 58.66±11.75 years, with the youngest patient being 27 years old and the oldest patient 87 years old. Among all patients, 19.20% were younger than 50 years, while 80.80% were older. Positive peritoneal lavage or peritoneal implants were found in 83.80% of cases. The histological types of tumors and their representation in the examined histopathological sample are shown in **Table 1**.

Regarding malignancy grade, tumors were categorized as high or low grade (G1, G2, G3). Among the examined samples, 17.17% were classified using the three-tier grading system (G1: 17.65%, G2: 47.06%, G3: 35.29%). The remaining tumors (67.68%) were classified using the two-tier system (high/low grade), with the majority of tumors (91.04%) being high grade and the rest (8.96%) low

Table 1. Presentation of histological types of ovarian cancers in the examined sample
Tabela 1. *Prikaz histoloških tipova ovarijalnih karcinoma u ispitivanom uzorku*

		N/*Br.*	%
Histological types of cancer *Histološki tipovi karcinoma*	Serous carcinoma/*Serozni karcinom*	71	71.72
	Mucinous carcinoma/*Mucinozni karcinom*	11	11.11
	Endometrioid carcinoma/*Endometrioidni karcinom*	6	6.06
	Mucinous borderline tumor/*Mucinozni 'borderline' tumor*	4	4.04
	Serous borderline tumor/*Serozni 'borderline' tumor*	2	2.02
	Clear cell carcinoma/*'Svetloćelijski' karcinom*	2	2.02
	Seromucinous borderline tumor/*Seromucinozni 'borderline' tumor*	1	1.01
	Undifferentiated or dedifferentiated carcinoma *Nediferentovani ili dediferentovani karcinom*	1	1.01
	Carcinosarcoma/*Karcionosarkom*	1	1.01
	Total/*Ukupno*	99	100

Table 2. Absolute and percentage values of carcinoma bilaterality, ovarian capsule involvement, uterine tube involvement, and application of neoadjuvant therapy
Tabela 2. *Prikaz apsolutnih i procentualnih vrednosti bilateralnosti karcinoma, zahvaćenosti kapsule jajnika, jajovoda i primene neoadjuvantne terapije*

		N/*Br.*	%
Bilaterality/*Bilateralnost*	No/*Ne*	44	44.40%
	Yes/*Da*	55	55.60%
	Total/*Ukupno*	99	100%
Capsule involvement/*Zahvaćenost kapsule*	No/*Ne*	40	40.40%
	Yes/*Da*	59	59.60%
	Total/*Ukupno*	99	100%
Tube involvement/*Zahvaćenost jajovoda*	No/*Ne*	72	72.70%
	Yes/*Da*	27	27.30%
	Total/*Ukupno*	99	100%
Neoadjuvant therapy/*Neoadjuvantna terapija*	No/*Ne*	95	96%
	Yes/*Da*	4	4%
	Total/*Ukupno*	99	100%

Table 3. Peritoneal dissemination rate depending on tumor bilaterality and ovarian capsule involvement
Tabela 3. *Učestalost peritonealne diseminacije bolesti u zavisnosti od bilateralnosti tumora i prisustva kapsularne invazije*

		Bilaterality/*Bilateralnost*						p/*p*
		No/*Ne*		Yes/*Da*		Total/*Ukupno*		
		N/*Br.*	%	N/*Br.*	%	N/*Br.*	%	
Peritoneal dissemination of the disease *Peritonealna diseminacija bolesti*	No/*Ne*	14	31.80	2	3.60	16	16.20	≤0.05
	Yes/*Da*	30	68.20	53	96.40	83	83.80	
	Total/*Ukupno*	44	100	55	100	99	100	
		Ovarian capsule involvement *Zahvaćenost kapsule jajnika*						p/*p*
		No/*Ne*		Yes/*Da*		Total/*Ukupno*		
		N/*Br.*	%	N/*Br.*	%	N/*Br.*	%	
Peritoneal dissemination of the disease *Peritonealna diseminacija bolesti*	No/*Ne*	14	35	2	3.40	16	16.20	≤0.05
	Yes/*Da*	26	65	57	96.60	83	83.80	
	Total/*Ukupno*	40	100	59	100	99	100	

Table 4. Analysis of the differences between peritoneal dissemination of the disease and the number of removed lymph nodes. Analysis of the differences between peritoneal dissemination of the disease and the number of lymph nodes exhibiting metastatic changes
Tabela 4. *Ispitivanje postojanja razlike između peritonealne diseminacije bolesti i broja odstranjenih limfnih čvorova. Ispitivanje postojanja razlike između peritonealne diseminacije bolesti i broja metastatski izmenjenih limfnih čvorova*

Average number of removed lymph nodes in regard to peritoneal dissemination of primary disease *Prosečan broj odstranjenih limfnih čvorova u odnosu na peritonealnu diseminaciju primarne bolesti*			
Peritoneal dissemination of the disease *Peritonealna diseminacija bolesti*	Average number of removed lymph nodes *Prosečan broj odstranjenih limfnih čvorova*	Mann Whitney *Man-Vitnijev test* (U)	p/*p*
Yes/*Da*	3.27	1057.500	0.510
No/*Ne*	1.92		
Peritoneal dissemination of the disease *Peritonealna diseminacija bolesti*	Average number of removed lymph nodes with confirmed metastasis/*Prosečan broj odstranjenih limfnih čvorova sa potvrđenim metastatskim promenama*	Mann Whitney *Man-Vitnijev test* (U)	p/*p*
Yes/*Da*	2.00	896.000	0.01
No/*Ne*	0.06		

grade. Fifteen tumors did not have an indicated malignancy grade. When comparing disease staging, the most prevalent stage was T3 (50%), followed by T1 (30.00%), and T2 (18.90%). T4 stage was the least represented (1.10%). Nine tumors did not have an indicated T stage in the medical records.

Table 2 presents absolute and percentage values of bilateral tumor presence, capsule involvement, uterine tubal involvement, and application of neoadjuvant therapy in the examined sample.

There was no statistically significant difference between the age groups (cutoff 50 years) and positive peritoneal lavage/implants (p=0.620). Patients with G1 malignancy grade did not have peritoneal disease expansion, whereas in patients with G3 grade, only one patient did not have peritoneal dissemination. Among patients with G2 malignancy grade, 62.50% had peritoneal dissemination. In stages T2, T3, and T4, no patients were without peritoneal dissemination, making it impossible to determine statistical significance.

Table 3 shows the frequency of peritoneal dissemination in relation to tumor bilaterality and ovarian capsule involvement.

Table 4 examines statistically significant differences in the existence of peritoneal dissemination and the number of the removed lymph nodes, as well as the number of lymph nodes with metastatic changes.

Discussion

The mean age of patients in our study was 58.66 years. Among the examined sample, 19.20% were younger than 50 years, while 80.80% were 50 years of age and older. Antonijević et al. [21] noted a rapid increase in new cases of ovarian cancer after the age of 40, with 78.80% of new patients falling between the ages of 40 to 74 years, 9.00% below 40 years, and 12.30% older than 75 years.

In our study, 83.80% of the patients tested positive for peritoneal expansion of malignancy, while 16.20% tested negative. Ayhan et al. reported that 31.40% of

patients initially diagnosed with early stage carcinoma were subsequently reclassified to higher stages due to findings of the occult peritoneal metastasis [18]. Serous carcinoma was more commonly associated with positive peritoneal cytology (76.90%) compared to the mucinous and endometrioid types (44% and 25%, respectively) [22]. The most prevalent histological type of carcinoma in our study was serous ovarian adenocarcinoma, accounting for 59.60% of cases. Similar percentage for serous adenocarcinoma (52%) was reported in the investigation by Torre et al. [23].

Regarding the histological grade, high-grade carcinomas were far more common in our study (91.04%), with low-grade tumors present in 8.96% of cases. Among the three-tier grading system, G2 histological grade was most prevalent at 47.06%, followed by G1 at 17.65% and G3 at 35.29%. In contrast, Plaxe reported different proportions in a study of 12,400 women, with G1 grade at 6.30%, G2 at 23.10%, and G3 at 57.50% of ovarian cancers, indicating a notable difference compared to our findings [24].

Regarding the bilateral presence of tumors on the ovaries, our study found that the tumor process was bilateral in 55 patients (55.60%), while in 44 patients, the malignant process affected only one ovary (44.40%). Boger-Megiddo et al. reported that serous ovarian adenocarcinoma is bilateral in 57.50% of cases [25]. In our study, 40 patients (40.40%) exhibited tumors affecting the ovarian capsule, while in slightly more cases (59.60%), there was no invasion of the ovarian capsule by the primary tumor. Naz et al. noted tumors on the ovarian capsule in 61.00% of medical findings, with omental metastasis observed in 51% of cases [22]. Examining fallopian tube involvement in ovarian carcinoma, it was determined that in most cases, there was no expansion to the fallopian tube. A higher percentage of tumor involvement in the fallopian tubes was described in a study conducted by Seidman et al. [26].

Regarding differences in peritoneal spread of the disease in relation to the age of patients, we found no statistically significant differences between peritoneal spread and patient age. The mean age of patients with low-grade carcinoma in study by Wafa et al. was 48 years (ranging from 26 to 76 years) [27].

In cases when the tumor process was bilateral, we observed a statistically significant relationship between peritoneal dissemination of the disease and the presence of bilateral ovarian tumor masses. We arrived at a similar conclusion when comparing peritoneal dissemination of the disease with invasion of the ovarian capsule by primary carcinoma. Naz et al. also determined a statistically significant correlation of capsular invasion with the presence of malignant peritoneal dissemination [22].

When comparing the differences in the number of extirpated lymph nodes and the number of lymph nodes with metastatic deposits in case of peritoneal dissemination of the disease, we observed no statistically significant difference in the former (Mann-Whitney test; U=1057.500; p=0.510). However, there was significant difference in the average number of removed lymph nodes with verified metastasis (Mann-Whitney test; U=896.000; p=0.01). Tsuruchi et al. concluded that there is a strong correlation between intraperitoneal dissemination and lymph node involvement [7].

It is evident that the process of malignant cell metastasis from the surface of the ovary to the peritoneal mesothelium is complex [28]. High concentrations of the vascular endothelial growth factor (VEGF) are found in peritoneal effusion of patients with ovarian cancer [29]. The expression of VEGF is also associated with ovarian carcinoma, secretion, matrix metalloproteinase (MMP) activity, tumor growth, invasion, and worse prognosis [30].

E-cadherin is an intracellular molecule that maintains and stabilizes intercellular connections [31]. Decreased expression of E-cadherin is associated with metastatic disease and increased mortality from ovarian carcinoma [32]. Cancer antigen 125, a glycoprotein overexpressed on malignant cells, it is known to bind to mesothelin expressed on mesothelial cells [33]. E-cadherin is again overexpressed during the implantation of malignant cells into the peritoneum, whereas its expression is reduced during cell detachment from the primary tumor mass [34].

Mesothelial cells respond to inflammation and malignant cell activity by secreting reactive forms of oxygen, interleukin 1, interleukin 6, and interleukin 8 [35]. Interleukin 1β can contribute to tumor angiogenesis and increased formation of peritoneal effusion by stimulating VEGF secretion [36]. Interleukin 6 can promote tumor migration, adhesion to mesothelium, and proliferation of malignant cells. It is also associated with shortened disease remission and overall worse prognosis [37]. Interleukin 8 is a proinflammatory mediator with proangiogenic effects that may stimulate tumor growth and invasiveness [38].

Conclusion

Based on our examined data and statistical analysis of the study, we can conclude that the occurrence of positive peritoneal lavage or peritoneal implantations is not dependent on the age of the participants. Additionally, we found no correlation between peritoneal dissemination of the carcinoma and the histological grade of malignancy. While there was no significant difference observed in the number of extirpated lymph nodes between patients with or without peritoneal dissemination, there was a significant difference in the average number of removed lymph nodes with verified metastasis in patients with positive peritoneal dissemination of the disease. However, several markers suggest that clinicians should persist in testing and obtaining information to determine if the carcinoma has peritoneally disseminated. The presence of bilateral tumor process and invasion of the ovarian capsule strongly indicate peritoneal dissemination of the disease. Early diagnosis is often challenging but should be a priority, similar to other malignant diseases, as it facilitates early initiation of therapy and improves survival rates.

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ANALYSIS OF THE HEALTH CARE SYSTEM IN THE REPUBLIC OF SERBIA: CROSS-SECTIONAL STUDY FOR THE YEAR 2021

ANALIZA ZDRAVSTVENOG SISTEMA REPUBLIKE SRBIJE – STUDIJA PRESEKA ZA 2021. GODINU

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Summary

Introduction. Through the analysis of a country's healthcare system, critical areas can be identified to enhance its development and ensure adequate healthcare provision for insured individuals. This study aims to assess the level of development of the healthcare system in the Republic of Serbia by analyzing selected indicators and identifying key issues impeding its progress. Given the scarcity of data in existing literature on this subject, we have chosen to analyze the healthcare system for the year 2021, particularly considering it as a period immediately following the COVID-19 pandemic and subsequent lockdowns. **Material and Methods.** Given the multifaceted nature of the research problem, the historical method was employed to illustrate the evolution and past reforms within the healthcare system of the Republic of Serbia. Additionally, content analysis was utilized to interpret existing literature within the relevant scientific domain, alongside quantitative data sourced from national and international databases. **Results.** This paper highlights key aspects of the development of the healthcare system of the Republic of Serbia, focusing on critical areas of action such as prevention, detection, flexibility, technical efficiency, legal regulation, and risk factors. **Conclusion.** Despite the Republic of Serbia ranking 25th in the region and 43rd in Europe according to the global index of health security, strategic approaches are necessary to stimulate reforms and enhance the health culture of the population through the implementation of precisely defined strategies.

Key words: Health Care Surveys; Delivery of Health Care; Quality of Health Care

Sažetak

Uvod. Analizom stanja zdravstvenog sistema jedne države moguće je identifikovati kritične tačke u svrhu unapređenja razvoja zdravstvenog sistema i mogućnosti pružanja adekvatne zdrastvene zaštite osiguranicima. Cilj ove studije je da ispita nivo zdravstvenog sistema Republike Srbije, analizom odabranih indikatora i identifikovanjem ključnih problema koji koče razvoj zdravstvenog sistema. S obzirom da u nama dostupnoj literaturi nedostaju podaci iz ove oblasti, odlučili smo se da izvršimo analizu zdravstvenog sistema za 2021. godinu, a posebno imajući u vidu da se radi o vremenskom periodu neposredno nakon pandemije COVID-19 i lokdauna. **Materijal i metode.** Kako kompleksnost zdravstvenog sistema jedne države podrazumeva analizu velikog broja elemenata i faktora, primenjen je istorijski metod sa ciljem da se prezentuje tok razvoja i sprovedenih reformi u zdravstvenom sistemu Republike Srbije. Analiza sadržaja je primenjena sa ciljem obrade dostupnih činjenica iz literature iz relevantne naučne oblasti, kao i dostupnih kvantitativnih podataka iz nacionalnih i međunarodnih baza podataka. **Rezultati.** Sagledavajući ključne oblasti delovanja – prevenciju, detekciju, fleksibilnost, tehničku efikasnost, zakonsku regulativu i faktore rizika zdravstvenog sistema Republike Srbije, u ovom radu je ukazano na kritične ključne aspekte zdravstvenog sistema. **Zaključak.** Iako globalni indeks zdravstvene sigurnosti pokazuje da je Republika Srbija na 25. mestu u regionu i 43. u Evropi po stepenu razvijenosti zdravstvenog sistema, neophodan je strateški pristup kako bi se podstakle reforme i unapredila zdravstvena kultura stanovništva, sprovođenjem precizno definisanih strategija.

Ključne reči: analize zdravstvenog sistema; pružanje zdravstvene zaštite; kvalitet zdravstvene zaštite

Introduction

The end of 2021 and the COVID-19 pandemic was a period characterized by significant uncertainty and concern regarding the ability of health systems and the populations to effectively respond to recurring pandemic challenges. [1].

Analyzing a nation's healthcare system provides critical insights into its development and capacity to deliver healthcare services. The comprehensive scope demands healthcare systems to be universally accessible, ensuring high-quality healthcare provision anytime and anywhere. This paper underscores the interconnectedness of various healthcare system components, evaluating their development level and collective impact on system effectiveness, including the organization and functioning of healthcare institutions and public perception towards the healthcare system.

The primary objective of this paper is to assess the present condition and level of advancement of

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Abbreviations

GHS index	– Global Health Security Index
EU	– European Union
WHO	– World Health Organization
HRH	– human resources for health

the healthcare system in the Republic of Serbia through the analysis of pertinent indicators. The imperative derived from this primary goal is to identify the principal obstacles impeding the progress of the healthcare system in Serbia.

Material and Methods

The study employed a blend of qualitative and quantitative analysis methods. Qualitative approaches encompasses the historical method and unstructured observational descriptive method, involving an examination of available documentation and data concerning the healthcare system of the Republic of Serbia, particularly focusing on the post-COVID-19 pandemic and associated lockdown measures. An electronic document review was conducted across various databases such as PubMed, Kobson, Scindeks, and Google Scholar, employing quantitative statistical methods. Furthermore, publications from reputable sources including the World Health Organization (WHO), Ministry of Labor, and Ministry of Health were integrated. Given the nature of this study, descriptive methods were essential for elucidating pertinent information about the healthcare system, not only within the domestic context but also across Europe.

Therefore, this study aims to underscore the significance and urgency of healthcare system development. By conducting both qualitative and quantitative analyses, it will provide insights into the current level of development and evaluate the state of the healthcare system in the Republic of Serbia. The social relevance of this research lies in identifying the attained level of development in the healthcare system of the Republic of Serbia and highlighting the primary challenges encountered by the healthcare sector.

Results and Discussion

The Healthcare System and the Imperative for Development

The World Health Organization defines healthcare and delineates its primary objective as "undertaking activities that ensure the promotion, restoration, and maintenance of health" [2]. In recent years, this objective has expanded to encompass the prevention of poverty, acknowledging the direct link between poverty and illness. Consequently, there is a recognized need for activities and measures focused on preserving public health through prevention, control and early detection of health disorders, along with engagement in terms of treatment and provision of adequate healthcare [3].

In the Republic of Serbia, the healthcare system comprises institutions operating at primary, secondary and tertiary levels to ensure public health. At the primary level, health centers play a crucial role, along with other facilities accessible without referrals. Hospitals constitute the secondary level, while clinical centers, institutes and clinics provide care at the tertiary level [4].

Nevertheless, discussions about healthcare quality increasingly emphasize desirable attributes such as efficiency, comprehensiveness, fairness, availability and satisfaction [5]. Upholding these standards necessitates a healthcare system equipped with skilled and educated personnel, as well as adequate financing for system development, particularly for adopting and implementing modern technological solutions that contribute to overall societal progress.

Achieved Level of the Healthcare System Development in the Republic of Serbia

The notable development of Serbia's healthcare system can largely be attributed to the democratic changes that took place at the end of 2000. A pivotal reform was introduced with the enactment of the Law on Health Records and Reporting in the Field of Health, enabling every patient to have an electronic health record, thereby modernizing and streamlining healthcare practices [6].

To analyze the achieved level of development of the healthcare system in the Republic of Serbia, data from the Global Health Security Index (GHS index) will be utilized in this paper. This index is compiled based on data reported by individual countries, emphasizing the importance of transparency in healthcare systems and the necessity for citizens to be informed about crucial information regarding existing capacities and future development plans. The questionnaire used to construct the index comprises 140 questions categorized into six groups, collectively assessing the development of healthcare systems. According to the most recent available data, the Republic of Serbia is ranked 25th in the region and 43rd in Europe in terms of the healthcare system's level of development [7].

Prevention

Preventive measures aim to promote healthy lifestyles and eradicate harmful habits that contribute to health deterioration. To highlight the importance of prevention, three indicators were analyzed: antimicrobial resistance, biological safety, and immunization.

Antimicrobial resistance refers to microorganisms' ability to resist antimicrobial agents, such as antibiotics. Serbia ranks 22nd in this indicator due to the adoption of a national plan for antimicrobial resistance, which led to a reduction in antibiotic consumption by over 30% from 2015 to 2017. Additionally, the Republic of Serbia introduced a national antibiotic resistance control program for the period 2019–2021 in 2019 [8].

In terms of biological safety, Serbia holds a notable position of 21st with an index of 50, attributed to clearly defined legislation on biological safety. The Law on Safety and Health at Work [9] regulates occupational safety and health, while the Rulebook on Preventive Measures for Safe and Healthy Work with Biological Hazards outlines minimum requirements for employers.

Regarding immunization, Serbia achieves a remarkably high score. With an index of 88.6, Serbia ranks 123rd in terms of immunization coverage for diseases such as hepatitis B, Bacille Calmette-Guerin, diphtheria-tetanus-acellular pertussis/inactivated polio vaccine/haemophilus influenzae type b (DTaP/IPV/Hib), measles-mumps-rubella (MMR), oral polio vaccine (OPV), and diphtheria-tetanus (DT) [10].

Disclosure and Reporting

The healthcare system's capacity for early detection and reporting of outbreaks of potential international concern consistently achieves a high observed index score, particularly in data integration and communication across different sectors **(Table 1).**

Laboratory systems within the healthcare sector have developed capabilities to conduct diagnostic tests for at least five of the ten basic tests outlined by the WHO. The Institute for Public Health of Vojvodina and the Institute for Blood Transfusion play crucial roles in this regard. Additionally, the Torlak Institute for Virology, Vaccines, and Serums is equipped to conduct viral culture testing, both during pandemics and under normal circumstances. Serbia excels in data integration and communication between systems, boasting a top-ranked index of 100 **(Table 2).** Furthermore, specific disease management has been enhanced through the efforts of the Commission for Clinical Guidelines and Good Practices, which established guidelines for major health conditions in 2010 [4].

Flexibility of the Healthcare System

The flexibility of the healthcare system is crucial for swiftly responding and implementing measures to curb the spread of epidemics or pandemics. Serbia ranks 38th among 195 countries in this regard. Operational teams, initiated by the Ministry of Health are established in the event of infectious disease epidemics. These teams oversee healthcare system activities, planning and coordination, communication, as well as monitoring and assessing the situation. These efforts were notably highlighted during the COVID-19 pandemic, where Serbia implemented rapid response measures, resulting in high rankings in these areas **(Table 3).** An example of this flexibility is the utilization of existing hospitals and public institutions' capacities, which were converted into COVID hospitals.

Technical Efficiency of Healthcare

Efficiency within the healthcare system is a crucial indicator of its performance and intermediate outcomes, with the ultimate goals being the health improvement of patients, alleviation of their com-

Table 1. Rating of public health prevention in Serbia
Tabela 1. *Ocena prevencije javnog zdravlja u Srbiji*

Indicator/*Indikator*	Index/*Indeks*	Rank*/*Rang*
Antimicrobial resistance/*Antimikrobna rezistencija*	44	22
Biological safety/Biološka sigurnost	50	21
Immunization/*Imunizacija*	88.6	123
*From a total of 195 countries/*Od ukupno 195 zemalja*		

Source: 2019 GHS Index Country Profile for Serbia, available at: https://www.ghsindex.org/country/serbia/ (20.05.2023)

Table 2. Rating of early detection and reporting of outbreaks in Serbia
Tabela 2. *Ocena ranog otkrivanja i izveštavanja o epidemijama*

Indicator/*Indikato*r	Index/*Indeks*	Rank*/*Rang*
Laboratory systems/*Laboratorijski system*	66.7	60
Real-time reporting/*Izveštavanje u realnom vremenu*	26.7	112
Data integration/*Integracija podataka*	100	1
*From a total of 195 countries/*Od ukupno 195 zemalja*		

Source: 2019 GHS Index Country Profile for Serbia, available at: https://www.ghsindex.org/country/serbia/ (20.05.2023)

Table 3. Flexibility rating of the healthcare system in Serbia
Tabela 3. *Ocena fleksibilnosti zdravstvenog sistema*

Indicator/*Indikator*	Index/*Indeks*	Rank*/*Rang*
Ability to react quickly/*Sposobnost brzog reagovanja*	25	38
Crisis response plan/*Plan odgovora u kriznim situacijama*	33.3	10
Risk communication/*Komunikacija o riziku*	100	1
Restrictions in pandemic conditions/*Restrikcije u uslovima pandemije*	100	1
*From a total of 195 countries/*Od ukupno 195 zemalja*		

Source: 2019 GHS Index Country Profile for Serbia, available at: https://www.ghsindex.org/country/serbia/ (20.05.2023)

Table 4. Efficiency rating of the healthcare system in Serbia
Tabela 4. *Ocena efikasnosti zdravstvene zaštite*

Indicator/*Indikator*	Index/*Indeks*	Rank*/*Rang*
Health facilities/*Zdravstveni kapaciteti*	19.4	101
Medical measures and work organization/*Medicinske mere i organizacija rada*	33.3	24
Access to health care/*Pristup u zdravstvenoj zaštiti*	45.9	53
Communication with healthcare employees during a pandemic *Komunikacija sa zdravstvenim radnicima u uslovima pandemije*	50	18
*From a total of 195 countries/*Od ukupno 195 zemalja*		

Source: 2019 GHS Index Country Profile for Serbia, available at: https://www.ghsindex.org/country/serbia/ (20.05.2023)

Table 5. Assessment of compliance with international standards
Tabela 5. *Ocena usklađenosti sa međunarodnim normama*

Indicator/*Indikator*	Index/*Indeks*	Rank*/*Rang*
Cross-border agreements in response to emergency situations *Prekogranični sporazumi kao odgovor na vanredne situacije*	100	1
International obligations/*Međunarodne obaveze*	46.9	81
Financing/*Finansiranje*	16.7	131
*From a total of 195 countries/*Od ukupno 195 zemalja*		

Source: 2019 GHS Index Country Profile for Serbia, available at: https://www.ghsindex.org/country/serbia/ (20.05.2023)

Table 6. Assessment of risk factors for the development of the healthcare system
Tabela 6. *Ocena faktora rizika razvoja zdravstvenog sistema*

Indicator/*Indikator*	Index/*Indeks*	Rank*/*Rang*
Political and security risk/*Politički i bezbedonosni rizik*	50	137
Socio-economic stability/*Socio-ekonomska stabilnost*	75.9	57
Infrastructure/*Infrastruktura*	66.7	46
Environmental risks/*Rizik javnog zdravlja*	48	124
*From a total of 195 countries/*Od ukupno 195 zemalja*		

Source: 2019 GHS Index Country Profile for Serbia, available at: https://www.ghsindex.org/country/serbia/ (20.05.2023)

plaints and extension of life [11]. Technical efficiency in healthcare correlates with treatment capacities for patients and accommodation capacities. In 2016, the density of hospital beds stood at 461.5 per 100,000 capita, while the average duration of acute care hospital stays per patient in 2014 was 8.4 days, exceeding the European Union average of 6.4 days [12]. The average hospital bed occupancy rate ranged from 80% to 85% between 2005 and 2006, decreasing to 68% in 2014, which is lower compared to the EU (77%) [12]. However, there is a shortage of beds in departments such as geriatrics and palliative care, indicating a healthcare system that struggling to adapt to current demands. This highlights the need for reforms focusing on primary and preventative care. as well as acute and long-term care services [13]. The Law on Health Care serves as the foundation of Serbia's healthcare system, ensuring comprehensive healthcare coverage for all citizens. Serbia's access to healthcare is rated at 45.9, positioning it in 53rd place **(Table 4).** However, access to secondary and tertiary care heavily relies on referrals from selected general practitioners, leading to significant waiting lists that hinder access to healthcare services [4].

Compliance with International Standards

The criterion of adherence to international standards encompasses activities aimed at enhancing and developing national capacities, financial planning for healthcare development and compliance with norms applied at both regional and international levels. Serbia has engaged in cross-border agreements with neighboring and European Union countries to facilitate immediate response during global disruptions to public health. However, a notable challenge pertains to healthcare system financing, which contributes to Serbia's low ranking in this aspect **(Table 5)** [4].

Risk Factors

The risk factors affecting healthcare system development encompass an evaluation of environmental conditions and the national economy's susceptibility to biological threats. Key factors include political and security risks, socioeconomic stability, infrastructure, environmental risks, and public health risks **(Table 6).** Assessing political and security risks involves evaluating government effectiveness, which received a notably low score (score 2), along with moderate scores for the risk of biological attacks and social unrest (score 3). Serbia ranks low in political and security risk assess-

ment, at 137th place. Socioeconomic stability significantly influences healthcare system development, with Serbia ranking 57th; poverty remains a major challenge, with well-established links between poverty and health outcomes across all communities [14]. The adverse effects of poverty on health, often leading to income loss due to illness-related work incapacity, are widely acknowledged [15]. Moreover, there's low citizen trust in competent institutions and inadequate work transparency [16]. Infrastructure quality remains subpar, hindering healthcare access, especially in rural areas. Environmental risk is notably high in Serbia [17, 18], significantly impacting various health conditions and environmental pollution [19].

Public health quality is measured by access to quality healthcare, living conditions, and public health expenditure. Data from the Institute for Public Health of Serbia "Dr. Milan Jovanović Batut" reveals that nearly one-fifth of residents aged over 15 in Serbia did not receive healthcare due to long waiting lists (15.4%), distance (4.1%), or financial constraints (31.3%). Financial limitations also hindered access to dental care (13.9%) and medical services (examinations, treatment, rehabilitation) (12.2%), along with the purchase of prescribed medications (9.9%) and mental healthcare (4%) [20].

Long waiting lists, particularly for diagnostic procedures (computed tomography, magnetic resonance imaging) and surgeries in orthopedics, ophthalmology, interventional cardiology, and cardiac surgery, contribute to healthcare unavailability. Nevertheless, research indicates that up to 91.1% of individuals aged 15 and above have a preferred doctor. Concerningly, approximately every eighth resident (12.5%) in the Region of South and East Serbia lacks a designated doctor in a state health institution. Conversely, 5.6% of the population has their own general practitioner or pediatrician in private practice, with higher percentages in Belgrade (10%), urban areas (6.4%), among the more educated (11.2%), and the wealthiest (11%) [20].

Discussion

The paper underscores the system's progress in prevention, disease detection, and adaptability to changes, signaling significant advancements compared to pre-reform periods. Nonetheless, the current funding mechanism fosters resource inefficiency and offers scant motivation for enhancing service quality and scope.

In recent years, Serbia has been implementing a program to improve and modernize the national healthcare system through the renovation and upgrading of equipment, as committed by the Serbian Government and in line with finances from international organizations such as the World Bank [21]. Human resources for health (HRH) is a priority issue not only in Serbia but globally. For healthcare systems worldwide, having a well-trained and capable workforce is crucial for achieving or maintaining accessible healthcare and improving health outcomes. Therefore, it is essential to dedicate special attention to the development and implementation of effective human resource management for health [22]. This essentially means that every country needs to invest in multisectoral efforts, complex mechanisms, and procedures to facilitate interaction between the government, service providers, and users. Although the healthcare system in Serbia entails compulsory health insurance for all and is financed based on a 10.3% payroll tax, 38% of healthcare expenditures in Serbia are still paid out-of-pocket. Regarding hospitals, despite the majority being state-owned, in Serbia, there has been significant growth and development in the private insurance and private healthcare service markets over the past decade [21]. According to the Regulation on the Health Institutions Network Plan in Serbia for the year 2019, there were a total of 3,509 healthcare institutions (35 pharmacies, 158 primary health care centers, 41 general hospitals, 34 specialized hospitals, 4 clinical hospital centers, 4 clinical centers, 7 clinics, 16 institutes, 25 public health institutes, 22 institutes, and 4 military institutions) [22]. Of all physicians in the Republic of Serbia, 5,309 (27%) were not specialists, among whom 2,754 (14%) were general practitioners and 2,555 (13%) were residents. The total number of specialists was 14,575 (73%) [22]. The total number of beds in state hospitals was 41,654, with 10% of the total number of physicians working in the private sector [23]. Considering the significant increase in the elderly population, poverty, chronic non-communicable diseases, climate disasters, and financial crises, policymakers should base their future directives on traditional policy pillars such as production, employment, and/or HRH management strategies. The COVID-19 pandemic emphasized the importance of ensuring safe and quality working conditions in the healthcare system, not only for healthcare workers but also for the entire population. Incorporating new guidelines and standards for workplace safety and quality assurance into the healthcare system is essential for attracting and retaining employees and addressing staff shortages. Patient and employee satisfaction with healthcare post-pandemic requires assessment, considering the challenges and strains faced by the healthcare system during the COVID-19 pandemic. Urgent attention is needed from policymakers to address these priority issues promptly and effectively.

Conclusion

Based on the analysis of available data from the Global Health Security Index, Serbia's healthcare system demonstrates strong development. However, shortcomings exist in disease detection and reporting, where Serbia lags in technology adoption for real-time reporting.

Despite the Republic of Serbia ranking 25th in the region and 43rd in Europe according to the global index of health security, strategic approaches are necessary to stimulate reforms and enhance the health culture of the population by implementing precisely defined strategies.

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CLINICAL CHARACTERISTICS OF COVID-19 IN FULLY VACCINATED VERSUS UNVACCINATED PATIENTS TREATED AT THE INFECTIOUS DISEASES CLINIC OF THE UNIVERSITY CLINICAL CENTER OF VOJVODINA

KLINIČKE KARAKTERISTIKE COVID-19 KOD KOMPLETNO VAKCINISANIH U ODNOSU NA NEVAKCINISANE PACIJENTE LEČENE NA KLINICI ZA INFEKTIVNE BOLESTI UNIVERZITETSKOG KLINIČKOG CENTRA VOJVODINE

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Summary

Introduction. COVID-19 vaccines have demonstrated high effectiveness in preventing hospitalization, severe disease and death. However, a minority of fully vaccinated adults still experience breakthrough infections. This study aims to evaluate the severity of breakthrough infections in the adult population. **Material and Methods.** A retrospective observational study was conducted from March 1, 2021, to June 30, 2021. We compared the clinical characteristics hospitalized patients who were fully vaccinated against SARS-CoV-2 with those who were not fully vaccinated. **Results.** During the study period, 216 patients were treated at the Infectious Diseases Clinic. Complete medical documentation was available for 120 patients, of which 20 (9.75%) were fully vaccinated. Vaccinated patients were older than unvaccinated patients (74 years vs. 60 years, p<0.001) and had a statistically higher prevalence of hypertension (p=0.004), previous cardiovascular diseases (p<0.001), and diabetes mellitus (p=0.014). A statistically significant higher proportion of bilateral pneumonias was observed in the unvaccinated group (p=0.042). The final outcome of the disease did not differ between the two groups. **Conclusion.** Our research confirmed that a significantly smaller percentage of vaccinated patients required hospital treatment, with vaccination coverage in the population during that period being around 50%. Fully vaccinated patients were generally older and had more chronic underlying diseases. While individual differences in the clinical presentation and course of the disease were observed between the groups, the results showed no difference in the final outcome.

Key words: COVID-19; SARS-CoV-2; Unvaccinated Persons; COVID-19 Vaccines; Signs and Symptoms; Hospitalization

Sažetak

Uvod. Vakcine protiv SARS-CoV-2 infekcije pokazale su visoku efikasnost u smanjivanju broja hospitalizacija, težih formi bolesti i letalnih ishoda. Manji udeo potpuno vakcinisanih odraslih oboleo je od COVID-19 infekcije. Cilj studije bio je da proceni karakteriske i težinu bolesti kod potpuno vakcinisanih pojedinaca. **Materijal i metode**. Sprovedena je retrospektivna opservaciona studija u periodu 1. 3. 2021−30. 6. 2021. godine u kojoj smo upoređivali karakteristike kliničke slike pacijenata koji su vakcinisani i onih koji nisu vakcinisani protiv SARS-CoV-2 a oboleli su i njihovo stanje je zahtevalo hospitalno lečenje. **Rezultati**. Za dati vremenski period na Klinici za infektivne bolesti lečeno je 216 pacijenata. Potpuna medicinska dokumentacija bila je dostupna za 120 pacijenata, od kojih 20 (9,75%) spada u grupu potpuno vakcinisanih obolelih i hospitalizovanih pacijenata. Vakcinisani pacijenti bili su stariji u odnosu na nevakcinisane (74 godine vs. 60 godina, p < 0,001), sa statistički značajno većim procentom hipertenzije (p = 0,004), prethodnim kardiovaskularnim događajima (p < 0,001) i dijabetesom melitus (p = 0,014). Potvrđen je statistički značajan veći udeo bilateralnih pneumonija kod nevakcinisane grupe (p = 0,042). Konačni ishod bolesti nije se razlikovao. **Zaključak.** Istraživanje je potvrdilo da je značajno manji procenat vakcinisanih pacijenata bilo neophodno hospitalizovati (u tom trenutku obuhvat vakcinacijom bio je oko 50% populacije). Potpuno vakcinisani pacijenti bili su stariji i opterećeniji hroničnim bolestima. Potvrđene su pojedinačne razlike u kliničkoj prezentaciji i toku bolesti između ispitivanih grupa, ali nije potvrđena razlika u krajnjem ishodu hospitalizovanih vakcinisanih i nevakcinisanih pacijenata.

Ključne reči: COVID-19; SARS-CoV-2; nevakcinisane osobe; COVID-19 vakcine; znaci i simptomi; hospitalizacija

Introduction

In December 2019, an increased incidence of atypical pneumonia of unknown etiology was observed in the city of Wuhan, Hubei Province, China. The situation, which began with sporadic cases, soon gained global proportions. The etiological

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Abbreviations

COVID-19	– Corona Virus Disease 2019
SARS-CoV-2	– Severe Acute Respiratory Syndrome Coronavirus 2
mRNA vaccines	– messenger RNA vaccines
UCCV	– University Clinical Center of Vojvodina
ARDS	– acute respiratory distress syndrome
IL-6	– interleukin-6
AST	– aspartate aminotransferase
ALT	– alanine aminotransferase
GGT	– gamma-glutamyltransferase
ICU	– Intensive Care Unit
CPAP	– continuous positive air pressure
ACE 2 receptors	– angiotensin-converting enzyme 2 receptors

agent, a virus, was identified as SARS-CoV-2, and the World Health Organization named the disease COVID-19 [1].

Despite a large number of patients exhibiting mild clinical symptoms, it has been shown that in some cases, the health condition of patients infected with SARS-CoV-2 progresses from pneumonia to acute respiratory distress syndrome (ARDS), which can potentially lead to disseminated intravascular coagulation, multiple organ dysfunction syndrome, and death [2–4]. Older age, male gender, and the presence of comorbidities such as hypertension and diabetes mellitus are risk factors for a more severe form of the disease [5, 6]. Subsequent studies of the pathogenetic mechanisms of the disease have indicated that a cytokine storm, part of the pathogenetic process, is responsible for severe forms and represents an excessive host response to infection, drawing parallels with certain occurrences in sepsis [7].

In 2020, a rapid global effort was undertaken to develop vaccines against SARS-CoV-2 infection. The goal was to increase population immunity through vaccination, thereby preventing severe forms of the disease and mitigating the ongoing health crisis worldwide [8]. This effort led to the development of new vaccine platforms, including vector vaccines, mRNA vaccines, and DNA vaccines [9]. In the Republic of Serbia, mass vaccination began in December 2020 (Official Gazette of the RS, No. 155/2020). The available vaccines included vector vaccines (Gam-COVID-Vac and ChAdOx1 nCOv-19), an mRNA vaccine (BNT162b2) and an inactivated vaccine (BBIBP-CorV) [10].

Large, multicenter randomized clinical trials published in the first half of 2021 showed encouraging results regarding the effectiveness of vaccination [8, 11–13]. An observational study by Haas et al. in 2021 demonstrated that vaccination contributed to a reduction in the incidence of SARS-CoV-2 infection, hospitalization, and deaths at the national level in Israel [14]. However, research has also documented cases of disease in fully immunized individuals, referred to as breakthrough infections [15, 16]. This study aims to compare the clinical characteristics, severity, course, and outcome of COVID-19 between fully vaccinated and non-vaccinated patients treated at the Infectious Diseases Clinic of the University Clinical Center of Vojvodina.

Material and Methods

This study includes patients treated at the Infectious Diseases Clinic of the University Clinical Center of Vojvodina (UCCV) from March 1, 2021, to June 30, 2021, with a confirmed diagnosis of COVID-19. Positive results were obtained from upper respiratory tract samples and confirmed by reverse transcription polymerase chain reaction and/or rapid antigen testing. Data on the subjects were retrospectively analyzed from available medical records, with the approval of the UCCV Ethics Committee (approval number: 00-150/2021).

Based on an epidemiological survey, patients were categorized into a fully vaccinated group and a control group of non-vaccinated subjects. Vaccinated patients confirmed anamnestically upon admission to inpatient care that they had received both recommended doses of one of the SARS-CoV-2 vaccines available in the Republic of Serbia, and that at least 14 days had passed since the second dose of the vaccine and the appearance of the first symptoms.

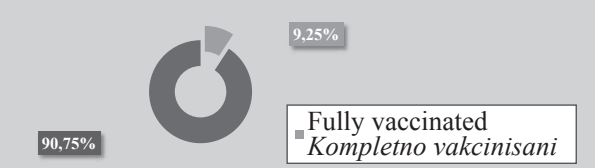
A total of 216 confirmed cases were treated at the Clinic during the specified period. Complete medical documentation was available for 120 patients at the time of data processing. The first group of completely vaccinated patients included 20 subjects, while the unvaccinated group consisted of 100 consecutive unvaccinated patients for whom complete medical documentation was available. Upon examination of the medical histories, data were obtained on age, sex, comorbidities, date of onset of symptoms, date of hospitalization, disease symptoms, use of antibiotic therapy before hospitalization, and the final outcome of hospitalization for all patients. The values of vital parameters at admission (body temperature measured axillary using a digital thermometer, pulse, respirations per minute, and systolic and diastolic blood pressure values), transcutaneous blood oxygen saturation (measured with a pulse oximeter) and lung X-ray findings were recorded. The following laboratory parameters were determined upon admission: complete blood count with leukocyte formula, C-reactive protein, procalcitonin, interleukin-6, fibrinogen, urea, creatinine, serum electrolytes (sodium and potassium), bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), activated partial thrombin time, prothrombin time, and D-dimer. Data on the course of treatment of patients (collected from the decursus) included information on the duration of fever in the hospital, implementation of the therapeutic protocol according to individual indications for each patient, admission to the Intensive Care Unit (ICU) and the length of treatment there, need for non-invasive ventilatory support (CPAP) and/or invasive mechanical ventilation together with the duration, the total length of hospitalization, and the final outcome of treatment (survived/deceased). All patients were treated according to the "Protocol for the treatment of patients with COVID-19" (versions 10 and 11) during the specified period. Information on

corticosteroid therapy (initial choice and dose of corticosteroids, length of intrahospital therapy, and whether the therapy was extended after discharge), low-molecular-weight heparin, types of antibiotics, oxygen therapy (whether it was received and its duration), intrahospital antibiotics, antiviral therapy (favipiravir), and immunomodulatory therapy (tocilizumab) was taken from the medical records for the purpose of the study.

For statistical data processing, SPSS software version 23.0 was used. Categorical variables are presented as n (%), and differences between groups were compared using the χ^2-test. By testing the normality of the distribution of continuous variables, it was concluded that most variables significantly deviate from the normal distribution. Accordingly, measures of central tendency of continuous variables are presented in percentiles (median and interquartile range), and differences between groups were compared by using the Mann-Whitney test. Statistically significant differences were those with $p<0.05$. The data are presented in tables and graphs.

Results

A total of 216 patients were treated at the Clinic during the specified period. Data on age, gender, and the final treatment outcome were available for all patients. There were 20 patients in the completely vaccinated group and 196 patients in the non-vaccinated group. Therefore, the vaccinated group accounted for 9.25% of those treated at the Clinic during the specified period, while the non-vaccinated group accounted for 90.75% **(Graph 1).**



Graph 1. Ratio of fully vaccinated and unvaccinated patients hospitalized at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021
Grafikon 1. *Udeo kompletno vakcinisanih među hospitalizovanim bolesnicima na Klinici za infektivne bolesti u periodu od 1. 3. 2021. do 30. 6. 2021. godine*

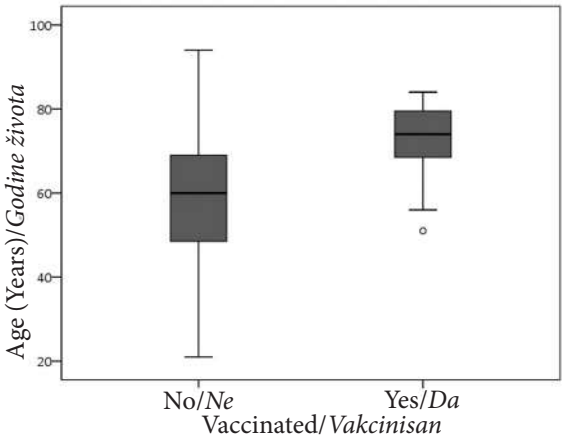
An analysis of the gender structure revealed that males were more prevalent among the hospitalized patients, but there was no statistically significant difference between the male and female genders between the two groups **(Table 1).** Vaccinated patients were statistically significantly older than non-vaccinated ones (74 years vs. 60 years, $p<0.001$), with a significantly higher prevalence of hypertension, previous cardiovascular diseases, and diabetes mellitus ($p=0.004$, $p<0.001$, $p=0.014$) **(Graph 2, Table 1).**

Table 1. Epidemiological characteristics, comorbidities, symptoms, vital parameters, laboratory analyzes, and lung X-ray findings in COVID-19 patients hospitalized at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021
Tabela 1. *Epidemiološke karakteristike, komorbiditeti, simptomi, vitalni parametri, laboratorijski nalazi i nalazi radiograma grudnog koša kod obolelih od COVID-19 hospitalizovanih na Klinici za infektivne bolesti u periodu 1. 3. 2021–30. 6. 2021.*

Characteristics/*Karakteristike*	Vaccinated/*Vakcinisani*		Total/*Ukupno*	p/*p*
	Yes/*Da**	No/*Ne**	N/*Br.* (%)	
Gender/*Pol*				
Male/*Muški*	13 (65)	124 (63.3)	137 (63.4)	0.878
Comorbidities/*Komorbiditeti*				
Obesity/*Gojaznost*	6 (30)	18 (18)	24 (20)	0.221
Hypertension/*Arterijska hipertenzija*	16 (18)	45 (45)	61 (50.8)	0.004
MI or stent */Akutni infarkt miokarda i/ili stent*	5 (25)	3 (3)	8 (6.7)	<0.001
COPD/*HOBP*	1 (5)	5 (5)	6 (5)	1.000
Autoimmune diseases/*Autoimune bolesti*	2 (10)	9 (9)	11 (9.2)	0.898
Malignant diseases/*Maligne bolesti*	1 (5)	6 (6)	7 (5.8)	0.898
Symptoms before hospitalization/*Simptomi pre hospitalizacije*				
Fever/*Temperatura*	20 (100)	92 (92)	112 (93.3)	0.190
Headache/*Glavobolja*	2 (10)	8 (8)	10 (8.3)	0.768
Muscle pain/*Mialgije*	1 (5)	6 (6)	7 (5.8)	0.862
Back pain/*Bolovi u leđima*	1 (5)	7 (7)	8 (6.7)	0.743
Sore throat/*Gušobolja*	3 (15)	9 (9)	12 (10)	0.414
Rhinorrhea/*Sekrecija iz nosa*	2 (10)	3 (3)	5 (4.2)	0.153
Cough/*Kašalj*	14 (70)	74 (74)	88 (73.3)	0.712
Dyspnea/*Dispnea*	6 (30)	27 (27)	33 (27.5)	0.784

Chest pain/*Bolovi u grudima*	8 (40)	2 (2)	10 (8.3)	0.000
Hemoptysis/*Hemoptizije*	0 (0)	3 (3)	3 (2.5)	0.433
Nausea/*Mučnina*	0 (0)	10 (10)	10 (8.3)	0.140
Vomiting/*Povraćanje*	1 (5)	5 (5)	6 (5)	1.000
Diarrhea/*Dijareja*	2 (10)	11 (11)	13 (10.8)	0.895
Anosmia/*Gubitak čula mirisa*	0 (0)	2 (2)	2 (1.7)	0.524
Highest fever/*Vrednosti najviše telesne temperature* (°C)	38 (37.8-39.0)	38.7 (38.2-39.0)		0.008
Duration of fever (days) *Trajanje povišene telesne temperature (dani)*	5.5 (3-8)	8 (5-10)		0.041
Vital parameters on admission/*Vitalni parametri pri prijemu*				
Body temperature/*Telesna temperature* (°C)	36.5 (36.5-37.8)	36.5 (36.5-37.7)		0.601
Systolic blood pressure/*Sistolni krvni pritisak* (mmHg)	130 (116-130)	120 (115-130)		0.394
Diastolic blood pressure/*Dijastolni krvni pritisak* (mmHg)	70 (66-80)	80 (70-80)		0.229
Heart rate/*Srčana frekvencija* (/min)	78 (67-90)	96 (81-106)		0.002
Respiratory rate/*Broj udaha u minuti* (/min)	16 (16-20)	16 (16-16)		0.335
Transcutaneous SpO_2/*Transkutana* SpO_2 (%)	96 (93-97)	96 (93-97)		0.925
Chest X-ray findings on admission/*Rendgenski nalaz grudnog koša pri prijemu*				
No pneumonia/*Bez pneumonije*	0 (0)	5 (5.2)	5 (4.3)	
Unilateral pneumonia/*Unilateralna pneumonija*	5 (25)	7 (7.3)	12 (10.3)	0.042
Bilateral pneumonia/*Bilateralna pneumonija*	15 (75)	84 (87.5)	99 (85.3)	
ARDS/*Akutni respiratorni distres sindrom*	0 (0)	0 (0)	0 (0)	
Laboratory parameters on admission/*Laboratorijski parametri pri prijemu*				
Leukocytes/*Leukociti* (10^9/l)	6.1 (5.3-9.5)	6.0 (4.4-7.6)		0.422
Neutrophils/*Neutrofili* (%)	81.1 (67.7-83.0)	79.8 (68.8-85.8)		0.869
Lymphocytes/*Limfociti* (%)	13.4 (9.1-22.72)	15.3 (9.5-23.7)		0.408
Monocytes/*Monociti* (%)	5.6 (2.8-8.1)	4.6 (3.3-6.5)		0.477
Eosinophils/*Eozinofili* (%)	0.2 (0.0-0.7)	0.0 (0.0-0.2)		0.004
Erythrocytes/*Eritrociti* (10^{12}/l)	4.1 (3.7-4.9)	4.7 (4.3-5.1)		0.007
Hemoglobin/*Hemoglobin* (g/l)	128 (117-145)	141 (128-150)		0.032
Thrombocytes/*Trombociti* (10^9/l)	163 (137-220)	190 (154-249)		0.120
C-reactive protein/*C-reaktivni protein* (mg/l)	77.8 (39.5-172)	56.2 (29.4-96.7)		0.218
Interleukin-6/*Interleukin-6* (pg/ml)	25.2 (9.6-44.3)	28.1 (13.1-52.1)		0.702
Procalcitonin/*Prokalciton* (ng/ml)	0.07 (0.0-0.6)	0.08 (0.0-0.2)		0.967
Urea/*Urea* (mmol/l)	7.5 (6.1-12.6)	5.5 (4.2-7.2)		<0.001
Creatinine/*Kreatinin* (µmol/l)	100 (84-126)	91 (73-108)		0.312
Sodium/*Natrijum* (mmol/l)	137 (135-142)	139 (136-141)		0.753
Potassium/*Kalijum* (mmol/l)	4.3 (3.8-4.6)	4.1 (3.8-4.4)		0.384
Total bilirubin/*Ukupni bilirubin* (µmol/l)	8.4 (5.8-11.3)	8.6 (6.6-11.5)		0.775
Direct bilirubin/*Direktni bilirubin* (µmol/l)	2.6 (2.0-4.2)	3.1 (2.5-4.4)		0.256
Aspartate aminotransferase/*Aspartat aminotransferaza* (U/l)	32.5 (30.0-37.5)	42 (33.5-61.0)		0.007
Alanine aminotransferase/*Alanin aminotransferaza* (U/l)	29.0 (23.5-45.7)	41.0 (32.5-67.5)		0.001
Gamma-glutamyltransferase/*Gama glutamil transferaza* (U/l)	29.0 (22.0-45.0)	38.0 (29.0-64.0)		0.043
Activated partial thromboplastin time (R) *Aktivisano parcijalno tromboplastinsko vreme (R)*	0.97 (0.82-1.07)	0.93 (0.85-1.00)		0.391
Prothrombin time/*Protrombinsko vreme* (R)	0.97 (0.90-1.02)	0.97 (0.92-1.04)		0.781
D-dimer/*D-dimer* (ng/ml)	1190 (720-1333)	835 (555-1120)		0.058
Fibrinogen/*Fibrinogen* (g/l)	5.7 (4.5-6.4)	6.2 (5.6-6.9)		0.086

Legend: COPD - chronic obstructive pulmonary disease; ACE2 receptors - angiotensin-converting enzyme 2 receptors;
*Categorical variables are presented as n (%), measures of central tendency of continuous variables are presented in percentiles (median and interquartile range)
Legenda: HOBP - hronična opstruktivna bolest pluća; ACE2 - angiotenzin konvertujući enzim 2 receptori;
**Kategorijalne varijable su predstavljene kao Br (%), mere centralne tendencije kontinuiranih varijabli su prezentovane kao procenti (medijana i interkvartilni raspon).*



Graph 2. Age structure of fully vaccinated and unvaccinated patients hospitalized at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021 (p<0.001)
Grafikon 2. *Starosna struktura kompletno vakcinisanih i nevakcinisanih pacijenata bolnički lečenih na Klinici za infektivne bolesti u periodu 1. 3. 2021–30. 6. 2021. (p<0.001)*

By examining the disease symptoms before admission to the hospital, a statistically significant difference between the vaccinated and non-vaccinated groups was recorded only for chest pain, which occurred more frequently in the vaccinated group (p<0.001), while the frequencies of other symptoms did not differ. Before hospitalization, non-vaccinated patients experienced a longer duration of fever (expressed in days) and higher body temperature values (p=0.041, p=0.008) **(Table 1).**

Radiological findings revealed a statistically significant difference (p=0.042) between the groups, with a higher proportion of bilateral pneumonia in the non-vaccinated group **(Table 1).**

Analysis of the complete blood count revealed that the mean values of erythrocytes, leukocytes, and platelets did not deviate from the reference values in either group. Although the values of erythrocytes and hemoglobin were slightly higher in the unvaccinated patients, this data is clinically irrelevant as they were within the range of reference values. A lower number of eosinophils was noted, which was more pronounced in the vaccinated group (p=0.004), while the degree of lymphopenia did not differ between the groups **(Table 1).** Urea values were statistically significantly higher in

Table 2. Therapy administered to patients treated for COVID-19 at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021
Tabela 2. *Primenjena terapija u lečenju COVID-19 na Klinici za infektivne bolesti u periodu 1. 3. 2021–30. 6. 2021.*

Characteristics *Karakteristike*	Vaccinated/*Vakcinisani*		Total/*Ukupno*	p/*p*
	Yes/*Da**	No/*Ne**	n/*Br.* (%)	
Intrahospital therapy/*Intrahospitalna terapija*				
Oxygen therapy/*Oksigenoterapija*	16 (80)	69 (69)	85 (70.8)	0.323
Corticosteroids/*Kortikosteroidi*	18 (90)	99 (99)	117 (97.5)	0.090
Favipiravir	2 (10)	2 (2)	4 (3.3)	0.690
Tocilizumab	8 (40)	44 (44)	52 (43.3)	0.742

*Categorical variables are presented as n (%)/*Kategorijalne varijable su predstavljene kao Br. (%).*

Table 3. Course of the disease and treatment outcome in COVID-19 patients treated at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021
Tabela 3. *Tok bolesti i ishod lečenja COVID-19 kod pacijenata bolnički lečenih na Klinici za infektivne bolesti u periodu od 1. 3. 2021. godine do 30. 6. 2021. godine*

Characteristics *Karakteristike*	Vaccinated/*Vakcinisani*		Total/*Ukupno*	p/*p*
	Yes/*Da**	No/*Ne**	n/*Br.* (%)	
Admission to the ICU/*Prijem u Jedinicu intenzivne nege*	4 (20)	21 (21)	25 (20.8)	0.920
CPAP	4 (20)	79 (79)	23 (19.2)	0.917
Mechanical ventilation/*Mehanička ventilacija*	4 (20)	8 (8)	12 (10)	0.102
Duration of hospitalization (days)/*Dužina hospitalizacije (dani)*	10 (7-16)	8 (7-11)		0.104
Duration of illness before hospitalization (days) *Dužina bolesti pre hospitalizacije (dani)*	7 (4-10)	9 (8-11)		0.033
Treatment outcome/*Ishod lečenja*				
Survived/*Preživeli*	3 (15)	21 (10.7)	24 (11.1)	0.561

Legend: CPAP - continuous positive air pressure
*Categorical variables are presented as n (%), measures of central tendency of continuous variables are presented in percentiles (median and interquartile range)
Legenda: CPAP – kontinuirani pozitivni pritisak vazduha u disajnim putevima
Kategorijalne varijable su predstavljene kao Br. (%), mere centralne tendencije kontinuiranih varijabli predstavljene su kao percentili (medijana i interkvartilni raspon).

the vaccinated group ($p<0.001$). The values of aspartate AST ($p=0.007$), ALT ($p=0.011$), and GGT ($p=0.043$) were statistically significantly higher in the unvaccinated group **(Table 1).** No significant difference was observed in other laboratory parameters between the groups.

The analysis of the use of antiviral and immunomodulatory therapy did not reveal statistically significant differences between the groups **(Table 2).**

The analysis of the duration of the disease (in days) before admission to inpatient care revealed a statistically significant difference ($p=0.033$), with non-vaccinated patients experiencing a longer period of illness before hospitalization in comparison to vaccinated ones. In examining the progression of the disease, no statistically significant differences were observed in the frequency of ICU admission, the need for non-invasive or invasive mechanical ventilation, or the length of hospitalization. Additionally, there was no statistically significant difference in the treatment outcome between the two groups **(Table 3).**

Discussion

The most important findings of our study include:

– The percentage of vaccinated individuals among hospitalized patients was 9.75%, while the percentage of vaccinated individuals in the general population at that time was 47.8%, according to official data from the Ministry of Health [17].

– Vaccinated patients who required hospitalization were statistically significantly older than non-vaccinated patients.

– Vaccinated patients who required hospitalization had a statistically significantly higher burden of comorbidities, including hypertension, cardiovascular issues (myocardial infarction or cerebrovascular insult), and diabetes mellitus.

– Although individual differences in the clinical presentation and course of the disease were noted, they did not statistically significantly differ between vaccinated and non-vaccinated hospitalized patients.

According to official data from the Ministry of Health, by mid-June 2021, 47.8% of the population in the Republic of Serbia had been fully immunized [17]. That percentage was significantly lower, only 9.75%, among hospitalized patients, clearly indicating the protective effect of vaccination in reducing the number of patients with a more severe clinical picture [18].

A study by Gustafsson et al. demonstrated that changes in signaling and communication between lymphocytes, along with a shorter lifespan of memory cells, could explain the reduced response of the elderly population to vaccination, known as immunosenescence [19]. In addition to the altered immune response to the vaccine, age-related changes in the immune system also lead to a chronic low-grade inflammatory state. Since older age correlates with a higher prevalence of comorbidities, these factors together indicate a reduction in the reserve capacity of vital organs, putting older individuals at high risk for severe disease outcome [5]. This conclusion explains the higher proportion of comorbidities such as hypertension, diabetes mellitus, or serious cardiovascular issues (e.g., acute myocardial infarction or coronary angioplasty) in the vaccinated group. Since both age and comorbidities are independent risk factors for COVID-19, and both were prevalent in the vaccinated population, it is logical that hospitalized fully vaccinated patients were older and chronically burdened with diseases compared to unvaccinated patients.

The interesting result regarding symptomatology differences, with an increased incidence of chest pain, was among the vaccinated group, may be linked to findings by Zhou et al. They note that cardiac complications (e.g., heart failure, new or worsening arrhythmia, acute myocardial infarction) are common in patients with pneumonia. Additional risk factors for cardiovascular issues following pneumonia include older age, preexisting cardiovascular comorbidities, and more severe pneumonia [20], all of which were prevalent in the vaccinated group. The higher incidence of anginal complaints in vaccinated patients can be interpreted as a potential worsening of cardiovascular status in the presence of SARS-CoV-2 infection. Additional clinical attention, including stricter monitoring of cardiovascular functions, is necessary for these patients to prevent unwanted cardiovascular complications.

The differences in the length of fever and the highest pre-hospital temperature can be understood in light of the age of the vaccinated population, which, as previously stated, was on average older. The geriatric population's response to infectious and inflammatory processes can be atypical, manifesting as confusion, falls, fatigue, incontinence and immobility [21]. The absence or reduction of fever could be an alternate response of the older vaccinated population to COVID-19. It would be unjustified to attribute these results to a potentially milder clinical presentation or reduced inflammatory processes due to vaccination, as the study focused on hospitalized patients with uniform criteria for hospitalization. Furthermore, as explained in the results, there were no significant differences in inflammatory laboratory parameters between the two groups. Rapid diagnosis and treatment of the geriatric population, considering the appearance of atypical symptoms, could prevent complications, shorten hospitalization and improve the quality of life for this age group [22].

In our analysis of radiological images at admission, we observed a higher percentage of bilateral pneumonia in the non-vaccinated population. The fact that the development of radiological findings is related to the duration of the disease since its onset can be a limiting factor of the results [23]. Our findings indicate that vaccinated patients were, on average, hospitalized earlier than non-vaccinated patients, which could partially affect the radiological findings at admission.

Laboratory analyses revealed elevated levels of urea in the serum of the vaccinated population. According to Ronco et al., renal dysfunction is common in COVID-19 patients, ranging from mild proteinu-

ria to acute renal failure, often occurring as part of multiple organ dysfunction syndrome requiring dialyses. Cardiovascular comorbidities and complications such as sepsis, hypovolemia, and nephrotoxins can impair renal function. COVID-19-induced heart failure may manifest as right-sided (causing renal congestion) or left-sided (leading to hypoperfusion), both of which could be pre-renal causes for elevated nitrogenous substances. The presence of ACE2 receptors in renal tissue may explain the direct renal impact of SARS-CoV-2 viremia [24]. The higher presence of cardiovascular comorbidities in the vaccinated group might explain the elevated urea levels, but we also observed that creatinine, another marker of renal function, did not follow this trend. The small sample size of vaccinated individuals may account for the limited specificity of these results. The isolated increase in urea may be due to SARS-CoV-2 binding to angiotensin-converting enzyme 2 receptors, activating the renin-angiotensin-aldosterone system, where water and sodium are absorbed, and causing passive reabsorption of urea from primary urine as a side effect [25]. Verified liver damage, indicated by increased aminotransferases, GGT and bilirubin activity, can predict more severe disease forms and worse outcomes [26, 27]. Potential liver and bile duct damage mechanisms include direct viral effects, cytokine storm, tissue ischemia and hypoxia, drug-induced liver injury or decompensation of pre-existing chronic liver disease [28]. The non-vaccinated group showed significant increases in AST, ALT and GGT upon hospital admission, with no significant differences in bilirubin levels. Since AST is found in tissues other than the liver (e.g., myocardium, skeletal muscles, kidneys), its value in interpreting the liver damage is less than that of ALT [27]. In severe COVID-19, which affects multiple organ systems, AST better reflects systemic damage. No differences were observed in the use of corticosteroids, favipiravir, tocilizumab, and oxygen therapy.

Conclusion

The similar results of Intensive Care Unit admission, need for ventilatory support, and final treatment outcomes suggest that the most severe disease forms were equally represented in both groups. However, this result should be considered in light of several factors, including the comparison of hospitalized patient numbers, age structure, and comorbidities in both groups. Although the qualitative characteristics of the hospitalization were similar, the quantitative characteristics favored the vaccinated population. Vaccinated patients were, on average, older and had more pre-existing conditions requiring inpatient treatment, while the younger population showed protection from more severe forms of Corona Virus Disease 2019 due to vaccination.

The reduction in severe disease among those over 50 years, decreased mortality rate, fever Corona Virus Disease 2019 hospitalizations, protection of the working-age population, reduction of absenteeism, indirect prevention of long Corona Virus Disease 2019 and decreased need for rehabilitation treatments are some of the conclusions drawn from this research. These findings also highlight the reduced burden on healthcare systems and decreased use of antimicrobial agents.

Limitations of this study include the small patient sample, its retrospective nature, and data collection limited to the Infectious Diseases Clinic, excluding other inpatient Corona Virus Disease 2019 treatment centers in University Clinical Center of Vojvodina.

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Erratum

In the double issue no. 7-8/2022, on page 224, in the Original studies section, in the paper titled:
THE IMPACT OF VOLUMETRIC ARC RADIOTHERAPY ON CLINICAL OUTCOMES OF PATIENTS WITH GYNAECOLOGICAL MALIGNANCIES
UTICAJ PRIMENE VOLUMETRIJSKI MODULISANE LUČNE RADIOTERAPIJE NA KLINIČKI ISHOD KOD PACIJENTKINJA LEČENIH OD GINEKOLOŠKIH KARCINOMA
Milijana RAKIN, Nataša ANIČIĆ, Olivera IVANOV, Sanja JARIĆ, Nemanja NOVAKOVIĆ and Ivan KORPIVICA

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The paper participants have noticed that they had made an unintentional mistake with the surname of the co-author Ivan Korpivica. We are hereby making a correction at their request, thus Ivan Korpivica should read Ivan KOPRIVICA.

Editorial Board

Erratum

U dvobroju 7-8/2022 na strani 224, rubrika Originalni naučni radovi, u radu pod naslovom:
THE IMPACT OF VOLUMETRIC ARC RADIOTHERAPY ON CLINICAL OUTCOMES OF PATIENTS WITH GYNAECOLOGICAL MALIGNANCIES
UTICAJ PRIMENE VOLUMETRIJSKI MODULISANE LUČNE RADIOTERAPIJE NA KLINIČKI ISHOD KOD PACIJENTKINJA LEČENIH OD GINEKOLOŠKIH KARCINOMA
Milijana RAKIN, Nataša ANIČIĆ, Olivera IVANOV, Sanja JARIĆ, Nemanja NOVAKOVIĆ and Ivan KORPIVICA

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Učesnici u radu su primetili da su napravili nenamernu grešku kod prezimena koautora Ivana Korpivice, te na njihovu molbu dajemo ispravku, tako da umesto Ivan Korpivica treba da stoji Ivan KOPRIVICA.

Uredništvo časopisa

CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
Prikaz slučaja
UDK 616.132-007.271-089.83
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RIGHT ANTERIOR MINITHORACOTOMY AND SUTURELESS AORTIC VALVE – A PERFECT MATCH

DESNA PREDNJA MINITORAKOTOMIJA I BEŠAVNA AORTNA VALVULA − SAVRŠEN SPOJ

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Summary

Introduction. Traditionally, surgical aortic valve replacement has been considered the gold standard for treating symptomatic patients with severe aortic stenosis. However, the development of transcatheter technology has introduced the concept of sutureless aortic valve replacement. As a result, minimal invasive aortic valve surgery is becoming increasingly popular and effective option in experienced centers, offering enhanced patient satisfaction and fewer complications. The utilization of sutureless valves has the potential to simplify and optimize aortic valve surgery by reducing the duration of the operation and facilitating prosthesis implantation. Nonetheless, there remain uncertainties regarding the optimal therapeutic choice, durability, and long-term outcomes. **Case Reports.** The case series involving 10 patients who underwent Perceval valve implantation demonstrated that the procedure was well-tolerated and yielded favorable outcomes. The surgery resulted in reduced implantation time and a decrease in complications. The patients experienced a postoperative course free from complications or cardiac rhythm disturbances, and they were discharged from the hospital on the fifth day of hospitalization. **Conclusion.** In essence, sutureless valves such as Perceval offer a promising solution for patients with aortic stenosis, particularly in the context of minimal invasive surgery. They can provide excellent hemodynamic performance, shorter the duration of the operation, and reduce hospital stay morbidity and mortality. However, long-term results and further research are necessary to definitively confirm their benefits.

Key words: Aortic Valve; Aortic Valve Stenosis; Thoracotomy; Heart Valve Prosthesis Implantation; Minimally Invasive Surgical Procedures; Treatment Outcome; Transcatheter Aortic Valve Replacement; Sutureless Surgical Procedures

Sažetak

Uvod. Hirurška zamena aortnog zaliska bila je zlatni standard za lečenje simptomatičnih pacijenata sa ozbiljnom aortnom stenozom. Međutim, razvoj transkateterske tehnologije uveo je koncept zamene aortnog zaliska bez šavova. Minimalno invazivna hirurgija aortnog zaliska postaje sve popularnija kao efikasna opcija u iskusnim centrima, pružajući veće zadovoljstvo pacijenata i manje komplikacija. Upotreba bešavnih zalistaka ima potencijal da pojednostavi i unapredi hirurgiju aortnog zaliska tako što smanjuje trajanje operacije i olakšava implantaciju proteze. Međutim, postoje nesigurnosti u vezi sa najboljim terapijskim izborom, trajnošću i dugoročnim rezultatima. **Prikaz slučajeva.** Serija slučajeva od 10 pacijenata koji su podvrgnuti implantaciji *Perceval* valvule pokazala je da je procedura dobro podnošljiva. Hirurgija je dala povoljne rezultate u smislu vremena implantacije i smanjenja komplikacija. Pacijenti su imali postoperativni tok bez komplikacija ili poremećaja srčanog ritma. Pušteni su kući petog dana hospitalizacije. **Zaključak.** U suštini, bešavne valvule, poput Percevala, nude obećavajuće rešenje za pacijente sa aortnom stenozom, posebno u minimalno invazivnoj hirurgiji. Mogu obezbediti odlično hemodinamičko ponašanje, kraće trajanje operacije i smanjenje morbiditeta i mortaliteta tokom boravka u bolnici. Međutim, dugoročni rezultati i dalja istraživanja su potrebni kako bi se definitivno potvrdile njihove prednosti.

Ključne reči: aortni zalistak; stenoza aortnog zaliska; torakotomija; implantacija proteze srčanog zaliska; minimalno invazivne hirurške procedure; ishod lečenja; transkateterska zamena aortnog zaliska; bešavne hirurške procedure

Introduction

The past decade has witnessed a notable interest in research focused on degenerative aortic stenosis, a condition whose incidence and prevalence continue to rise in Western countries [1]. With the aging population, aortic stenosis has become the most prevalent valvular heart disease in adults [2]. Surgical aortic valve replacement (AVR) remains the established standard for treating symptomatic patients with severe aortic stenosis, effectively restoring their life expectancy [3]. However, the presence

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Abbreviations

AVR	– aortic valve replacement
MI-AVR	– minimal invasive aortic valve replacement
MI	– mini-sternotomy
ART	– right anterior thoracotomy
ACC	– aortic cross-clamp
ICU	– Intensive Care Unit
AS	– aortic stenosis
ECC	– extracorporeal circulation
CPB	– cardiopulmonary bypass

of multiple comorbidities in older patients undergoing aortic valve surgery has led to the development of new valve implantation techniques aimed at reducing surgical risk [4].

The emergence of transcatheter technology in 2002 has introduced the concept of sutureless valve replacement, offering a novel approach to aortic valve replacement [5], which has been in clinical practice since 2008 [6]. In our region, the Perceval valve is the sole available sutureless valve for implantation, and it has demonstrated excellent short-term and mid-term outcomes with reduced implantation time [2].

Minimal invasive aortic valve replacement (MI-AVR) has gained traction as an effective choice for surgical treatment in well-established centers, providing higher patient satisfaction and fewer complications [4]. This is particularly relevant for older patients with multiple comorbidities, for whom minimizing overall risk and enhancing surgical outcome is paramount [7, 8]. A multidisciplinary patient-centered approach is essential for this group of patients as there are no standardized guidelines determining when to employ a minimally invasive approach [4]. The most common approaches for MI-AVR currently include the upper mini-sternotomy and right anterior thoracotomy (ART) techniques [9]. While both approaches offer various clinical benefits compared to the traditional sternotomy, the adoption of MI-AVR has been limited within the surgical community [10]. This may be attributed to the perceived increased surgical complexity associated with MI-AVR, which can result in longer operative times compared to conventional AVR [9]. However, the use of sutureless valves and their rapid deployment may help streamline and promote MI-AVR by simplifying and expediting the implantation process [11]. Sutureless valves can reduce the duration of the operation and facilitate easier prosthesis implantation through a limited approach, thereby mitigating some of the primary limitations of MI-AVR procedures, and they can be considered a primary choice in minimally invasive surgery [9]. However, uncertainties still exist regarding the optimal therapeutic selection, durability, and long-term outcomes [1].

Case Reports

The Perceval sutureless aortic valve was successfully implanted in 10 patients at the Institute of Cardiovascular Diseases of Vojvodina. These patients all presented with isolated valvular pathology in the form of severe aortic stenosis and were aged over 65. They comprised a mix of genders and exhibited varying Body Mass Index (BMI) values. Additionally, they presented with various comorbidities, including atrial fibrillation, diabetes, left bundle branch block, chronic obstructive pulmonary disease, and chronic kidney insufficiency. Preoperative echocardiographic examinations confirmed that all patients had a trileaflet aortic valve with severe aortic stenosis, accompanied with varying degrees of aortic regurgitation. Importantly, these examinations ruled out any contraindications for the implantation of the Perceval valve. None of the patients exhibited a dilated aortic root, and the relationship between the sinotubular junction and the diameter of the aortic annulus was less than 1.3 mm, eliminating the possibility of a dilated ascending aorta or aortic dissection.

In preparation for the minimally invasive approach, all patients underwent preoperative computed tomography aortography focused on understanding the relationships between the aortic valve, the sternum, and the intercostal spaces. In general, the relative dextroposition of the ascending aorta (at least 50% of the aortic width positioned to the right of the sternal edge at the level of the pulmonary bifurcation) and an appropriate depth of the aortic root, not exceeding 10 cm from the skin to the aortic annulus, provided an ideal surgical exposure for the right minithoracotomy.

Exclusion criteria for Perceval implantation through the ART approach included acute endocarditis, irregular aortic annulus or aortic anatomy, isolated aortic regurgitation, bicuspid aortic valve, severe chest deformities, adhesions of the right pleural cavity, or technical difficulties with peripheral percutaneous cannulation.

Prior to the intervention, informed consent was obtained from each patient. Premedication included administration of 3.75 mg of Midazolam orally and 1 mg of Atropine intramuscularly, half an hour before the intervention. Additionally, a 16 G intravenous cannula was placed for preoperative preparation, an arterial catheter was inserted into the left radial artery, and a central venous catheter was positioned in the right internal jugular vein. Following induction with Midazolam, Propofol, Sufentanyl, and Rocuronium, the patients were intubated using a double-lumen tube. A transesophageal echocardiography probe was also introduced.

The minimally invasive procedure was conducted through a right anterior thoracotomy via the second intercostal space. Following the longitudinal opening and pre-ventilation of both lung fields, the right lung was collapsed, and ventilation continued with "one-lung ventilation". The pericardium was suspended, and distal cannulation of the ascending aorta was performed, along with venous cannulation of the right atrium. An external aortic clamp was then directly applied to the aorta, and crystalloid cardioplegia was indirectly administered through an angiocatheter.

The procedure involved a transverse aortotomy, followed by the excision and decalcification of the

native valve leaflets. The Perceval valve, prepared for implantation, was initially placed on a holder and inserted into a collapsor of the corresponding size. By rotating the handle of the collapsor, the proximal and distal rings of the valve were collapsed while maintaining the integrity of the leaflets. The prepared valve was then immersed in warm physiological saline and stored until implantation. This method facilitated size reduction and enabled placement through a small incision without manipulation at the annulus level.

Prior to valve implantation, three guiding sutures were placed to ensure the proper positioning of the bioprosthesis. The holder containing the bioprosthesis was lowered into the aortic annulus until it reached the location where the guiding sutures were positioned. The next step involved releasing the holder and confirming the correct valve size, precise positioning, and full expansion. Following this confirmation, balloon dilation was performed to enhance valve adaptation and optimal sealing on the native aortic annulus. The balloon was inflated to 4 atmospheres for 30 seconds, while a stream of warm physiological saline was continuously directed into the aortic root to further secure the sealing of the aortic valve and fixation, considering the thermosensitive nature of the nitinol stent material.

Different valve sizes were implanted in our patients, with 4 patients receiving size S, 2 patients size M, 3 patients size L, and 1 patient size XL. Following the implantation of the bioprosthesis, the aortotomy was closed, and deaeration was conducted after tying the final suture. The heart was subsequently filled with blood, both lung fields were re-expanded, and the aortic clamp was released. The average duration of aortic cross-clamping (ACC) was 36 minutes, and extracorporeal circulation (ECC) lasted 43 minutes.

Transesophageal examination confirmed the accurate implantation of the prosthetic valve following the discontinuation of extracorporeal circulation. The patients were then reintubated with a single-lumen tube, and were hemodynamically and rhythmically stable as they were transferred to the Intensive Care Unit (ICU). On average, the patients were extubated 2 hours and 27 minutes after the completion of the operation. They spent one day in the ICU. The postoperative course progressed without any complications in all patients. As there were no instances of paravalvular leaks, rhythm disturbances, drainage, or revisions, the patients were discharged in good general condition on the 5th day of hospitalization.

Discussion

Aortic stenosis (AS) is the most prevalent valvular condition, leading to reduced life expectancy in symptomatic patients [12]. Aortic valve replacement (AVR) remains the primary therapeutic approach for managing these cases [13, 14]. Data from The Society of Thoracic Surgeons reveal a substantial improvement in AVR's operative risk over the past decade, reducing mortality rates from 4.3% to 2.6% [15]. However, despite these advancements, elderly patients and those with significant comorbidities referred for AVR continue to face unacceptably high perioperative risks and suboptimal outcomes, suggesting that innovative approaches such as sutureless valves could help mitigate mortality and morbidity [12].

The concept of sutureless aortic valve prostheses was originally introduced by Magovern and Cromie in the early 1960s [16]. Their objectives were to simplify aortic valve replacement, reduce surgical duration, and circumvent complications linked to prolonged cardiopulmonary bypass (CPB) and ACC times [15]. However, this groundbreaking idea was abandoned due to complications associated with the valve, including frequent perivalvular leaks, dehiscence in patients with enlarged aortic roots, and thromboembolic complications [17]. Advances in bioprosthetic technology have since resolved these initial challenges, with published data confirming promising results in terms of mortality, morbidity, and hemodynamic performance following the implantation of these sutureless valves [15].

The Perceval valve is a biological prosthesis comprised of bovine pericardium stabilized in a buffered glutaraldehyde solution and mounted on a nitinol stent [12]. It is available in various sizes: small, medium, large, and extra-large (S (19–21 mm), M (22–23 mm), L (24–25 mm), and XL (26-27 mm)) [8]. All our patients had the Perceval valve implanted. In cases of incorrect positioning during implantation, the Perceval valve can be safely removed, even after balloon dilation. If no malformations are observed in the prosthesis after the procedure, it can be reimplanted in the correct intra-annular position [15]. Three out of our ten patients required repositioning due to inadequate initial valve placement. Since no valve malformations were detected, successful reimplantation was performed without complications.

The advantages of sutureless bioprostheses include quicker implantation as there is no need for sewing the valve, along with reduced durations of CPB and ACC [12]. It is important to note that extended ACC and CPB times are associated with increased perioperative morbidity and mortality [18]. A meta-analysis by Sian et al. demonstrated that the Perceval valve significantly reduces ACC and CPB times compared to conventional AVR. The average ACC and CPB times for isolated AVR were 39.7 and 64.2 minutes, respectively, which were shorter than the established conventional AVR times of 76 and 106 minutes [2]. In our cases, the average aortic cross-clamp duration was 36 minutes, and the average CPB duration was 43 minutes. A study by Concistre et al. reported slightly longer CPB and ACC times, likely due to the surgical approach [14]. Solinas and colleagues reported an average CPB time of 81.6±30.8 minutes and an ACC time of 50.3±24.5 minutes [18].

The effective orifice area of sutureless valve prostheses is larger for any Perceval valve size than for conventional prostheses due to the absence of an an-

choring ring. This feature is particularly beneficial for patients with small aortic roots, which was the case for most of our patients [19]. Additionally, reduced surgical manipulation during sutureless aortic valve implantation and decreased presence of foreign material around the aortic annulus may offer advantages [1].

Adverse events related to sutureless valve implantation are minimal. Overall rates of reoperation (1.43%) and early infections (<1%) are low, further supporting favorable early outcomes with sutureless valves [2]. None of our patients required reoperation or experienced early infections. According to the meta-analysis by Sian et al. an acceptable early mortality rate of 2.1% and an incidence of strokes of 1.4% were reported after Perceval valve implantation, with no statistically significant difference compared to conventional aortic valves [2]. However, after Perceval valve implantation, there was an increased need for pacemaker implantation, 6.7% compared to 3.6% with conventional valves [2], a finding also confirmed by Solinas et al. who reported a need for pacemaker implantation in 5.2% of operated patients [18]. Nevertheless, a study by Gilmanov et al. showed that the intrahospital morbidity and mortality, incidence of postoperative strokes, as well as the need for pacemaker implantation were the same for sutured and sutureless valves [1]. Fortunately, our patients did not experience rhythm disturbances, undesired cerebrovascular events, or require pacemaker implantation after surgery. According to Solinas et al. the length of hospitalization for patients with implanted Perceval valves was 6.4±3.8 days [18]. All our patients were discharged on the 5th day of hospitalization.

In recent years, the focus on treating aortic valve pathology has shifted towards the development and promotion of minimally invasive procedures [20]. Sutureless valves offer a distinct advantage in this context, as they are well-suited for MI-AVR due to their ease of insertion with minimally invasive approaches [21]. The collapsible delivery system of these prostheses allows for optimal intraoperative exposure of the aortic root, even in patients with suboptimal anatomical conditions [8]. Typically, this procedure is performed through a right anterior mini-thoracotomy, which was the chosen approach for our patients [18]. Previously, this challenging approach was reserved for experienced surgeons due to the limited working space, restricted visibility, and deviations from the normal course, which deterred many surgeons from adopting it [1].

In comparison to standard median sternotomy, MI-AVR has been shown to yield superior clinical outcomes, including reduced postoperative complications, decreased blood loss and transfusion requirements, lower risk of reoperation due to bleeding, reduced postoperative pain, shorter ventilation times, shorter stays in the ICU, and overall hospital stays, faster return to functional activities, improved cosmetic appearance [9, 21], as well as enhanced patient satisfaction [2]. Despite these promising findings, the utilization of MI-AVR surgery remains disappointingly low, with most AVR interventions being still performed via full sternotomy [22].

However, despite the established benefits, there remains a lack of evidence regarding the long-term outcomes of sutureless aortic valve prostheses, highlighting the need for larger studies in this area [18].

Conclusion

Minimally invasive surgical approaches coupled with the implantation of sutureless valves synergistically present a less invasive treatment concept that may offer distinct advantages over traditional approach, particularly for older patients with elevated surgical risk and frailty indices. In addition to delivering excellent hemodynamic outcomes, these techniques contribute to shorter durations of cardiopulmonary bypass, decreased intrahospital morbidity and mortality rates, and heightened patient satisfaction, collectively providing promising results.

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Case report
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TRACHEAL INFLAMMATORY MYOFIBROBLASTIC TUMOR IN A 3-YEAR-OLD BOY

INFLAMATORNI MIOFIBROBLASTNI TUMOR TRAHEJE KOD TROGODIŠNJEG DEČAKA

Gordana VILOTIJEVIĆ DAUTOVIĆ[1, 2], Rajko JOVIĆ[1, 3], Nada VUČKOVIĆ[1, 4], Milena BJELICA[1, 2] and Milica PLAZAČIĆ[2]

Summary

Introduction. Inflammatory myofibroblastic tumors predominantly manifest in the lungs of children and young adults, with tracheal localization being very rare. Genetic alternations involving the anaplastic lymphoma kinase gene are identified in 50 to 70% of cases. A conclusive diagnosis relies on biopsy and histopathological analysis. Surgical resection stands as the primary treatment modality. **Case Report.** We present a case involving a 3-year-old boy with an inflammatory myofibroblastic tumor who had experienced recurrent wheezing attributed to respiratory infections since the age of eight months. Long-term therapy with budesonide and montelukast was initiated, which effectively managed his wheezing until the age of 3 years. Subsequently, despite ongoing medication, he began experiencing severe bronchial obstructions every month, necessitating repeated hospital admissions. At the age of 3 years and 8 months, he was admitted to our hospital due to persistent wheezing, prompting a bronchoscopy. During the procedure, a tumor-like mass was identified in the lower part of the trachea. Bronchoscopic removal of the tumor was performed, followed by cauterization of the remaining tumor tissue. Histopathological examination confirmed the presence of an inflammatory myofibroblastic tumor. **Conclusion.** Inflammatory myofibroblastic tumors are uncommon neoplasms associated with a borderline risk of malignancy. Given that the symptoms can resemble those of common childhood respiratory conditions, it is crucial to consider this diagnosis in cases of persisting wheezing despite standard therapy. In such instances, performing a bronchoscopy is necessary for accurate diagnosis.

Key words: Tracheal Neoplasms; Myofibroblasts; Bronchoscopy; Airway Obstruction; Respiratory Sounds; Child; Diagnosis, Differential

Sažetak

Uvod. Inflamatorni miofibroblastični tumori se najčešće javljaju u plućnom parenhimu dece i mladih odraslih, dok je njihova pojava u traheji veoma retka. Promene u genu za anaplastičnu limfomsku kinazu su potvrđene kod 50−70% pacijenata. Definitivna dijagnoza se postavlja na osnovu biopsije i patohistološke evaluacije. Osnovni vid terapije je hirurška resekcija tumora. **Prikaz slučaja.** Prikazan je inflamatorni miofibroblastični tumor traheje kod trogodišnjeg dečaka koji je imao epizode rekurentnog vizinga tokom respiratornih infekcija počev od osmog meseca života. Uvedena je terapija budesonidom i montelukastom i dečak je bio bez tegoba do treće godine života, nakon čega je imao je teške bronhoopstrukcije svakog meseca koje su zahtevale ponavljane hospitalizacije u lokalnoj bolnici. Kada je imao tri godine i osam meseci hospitalizovan je u našoj bolnici zbog perzistentnog vizinga. Sprovedena je bronhoskopija, opservirana je tumorska promena u donjem delu traheje. Načinjena je bronhoskopska ekstrakcija tumora uz kauterizaciju remnant tumora. Patohistološkim pregledom je potvrđen inflamatorni miofibroblastični tumor. **Zaključak.** Inflamatorni miofibroblastični tumori su retke neoplazme sa graničnim stepenom malignosti. Dijagnoza može biti maskirana simptomima i znacima najčešćih respiratornih bolesti u detinjstvu, poput rekurentnog vizinga kod predškolske dece. Bronhoskopiju treba uraditi kod svih pacijenata sa perzistentnim vizingom koji imaju neadekvatan klinički odgovor na standardnu terapiju.

Ključne reči: tumori traheje; miofibroblasti; brohnoskopija; opstrukcija disajnih puteva; respiratorni zvuci; dete; diferencijalna dijagnoza

Introduction

Inflammatory myofibroblastic tumors are rare neoplasms most commonly found in the lungs of children and adolescents [1, 2]. While they primarily occur in the lungs, they can also manifest in other extrapulmonary sites, though less frequently [2]. Additionally, inflammatory myofibroblastic tumor (IMT) is referred to by various terms in the literature, including plasma cell granuloma, inflammatory pseudotumor, inflammatory myofibrohistiocytic proliferation or inflammatory fibrosarcoma [3–5]. According to the World Health Organization's 2013 classification, myofibroblastic tumors are considered mesenchymal neoplasms of intermediate malignancy, exhibiting diverse histological and biological characteristics [1].

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Abbreviations

IMT – inflammatory myofibroblastic tumor
ALK – anaplastic lymphoma kinase
SMA – smooth muscle actin
COX-2 – cyclooxygenase-2

The etiology of IMTs remains unclear, but it is believed that these tumors arise from an aberrant inflammatory response triggered by various antigens. Changes in the anaplastic lymphoma kinase (ALK) gene have been observed in 50 to 70% of cases [6–8].

Clinical presentation of IMTs varies widely, with symptoms ranging from nonspecific laboratory and radiographic findings. A definitive diagnosis is established through biopsy and histopathological examination [6, 9, 10].

While surgical resection is the primary treatment modality, systemic therapies such as steroids, immunomodulators, radiotherapy, and chemotherapy may be considered for advanced or recurrent cases. Target therapy is an option for patients with confirmed ALK translocation [11–14].

Case report

The 3-year-old boy had a history of recurrent wheezing attributed to respiratory infections since the age of eight months and was managed with long-term asthma preventive therapy consisting of budesonide and montelukast. In addition to episodes of bronchial obstruction, the boy experienced periodic symptoms of allergic rhinitis. Further diagnostic evaluation revealed elevated IgE levels (305 IU/ml) and a positive skin prick test for tree pollen. Despite adhering to the regular asthma preventive therapy, the boy began experiencing severe bronchial obstructions on a monthly basis from the age of 3. These episodes necessiated repeated hospital admissions. As a consequence of persistent wheezing that did not respond to salbutamol inhalation, the boy was transferred from the local hospital to our institute.

Upon admission to our institute, the boy presented as afebrile, tachydyspnoic, and tachycardic, with a oxygen saturation of 96% on oxygen therapy delivered via a face mask at 6 liter per minute. Wheezing was heard on on chest auscultation, and a chest X-ray revealed perihilar inhomogeneous patchy infiltrates on the right side. Laboratory investigations showed leukocytosis (Le 26 G/L) and thrombocytosis (Tc 660 G/L), while blood gas exchange and electrolyte values remained within normal limits.

Initial management involved oxygen supplementation, inhaled salbutamol, corticosteroids (both inhaled and systemic), and antibiotic therapy. Persistent symptoms prompted further evaluation with bronchoscopy.

Fiberoptic tracheobronchoscopy under general anesthesia was initially performed by a respiratory pediatrician. During the procedure, a tumor-like mass was observed in the lower third of the trachea, situated on the lateral wall above the main carina and the right bronchus. The tumor occupied two-thirds of the trachea lumen and exhibited smooth surface that bled upon contact. It was attached to the trachea by a wide petiole. The fiberoptic bronchoscope was able to pass adjacent to the tumor, with the main carina appearing sharp, and the rest of the tracheobronchial tree showing no pathological changes. Subsequently, rigid tracheobronchoscopy was performed by an otorhinolaryngologist using a STORZ rigid bronchoscope (30 cm in length, size 5, with 0˚ telescope). The tumor change was visualized in the lower third of the trachea and removed using forceps. The dimensions of the tumor were 2 x 0.6 cm, and it exhibited a pale yellow color and firm consistency **(Figures 1 and 2).**

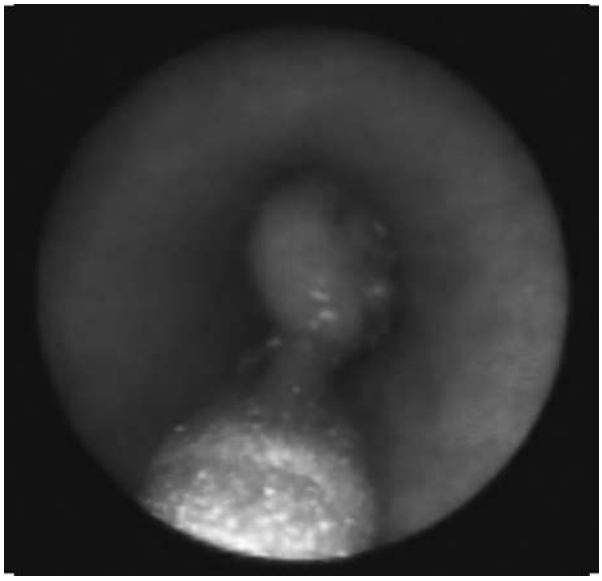

Figure 1. Bronchoscopic view showing the tracheal tumor arising from the lateral wall of the trachea
Slika 1. *Bronhoskopski prikaz tumorske promene lateralnog zida traheje*

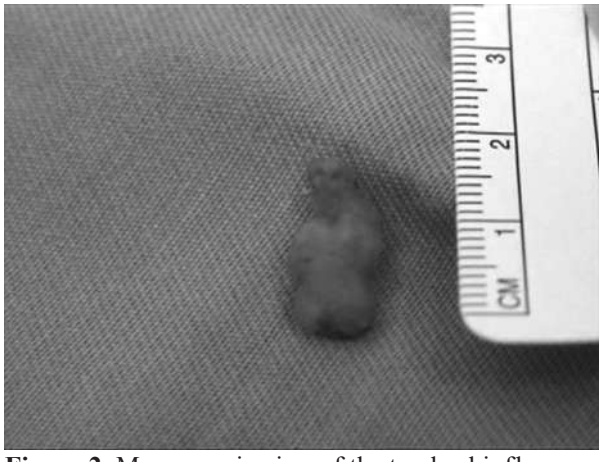

Figure 2. Macroscopic view of the tracheal inflammatory myofibroblastic tumor. The tumor surface is pale yellow color, appearing firm, measuring 2 x 0.6 cm.
Slika 2. *Makroskopski prikaz inflamatornog miofibroblastičnog tumora traheje. Površina tumora je svetložute boje, deluje čvrste konzistencije, dimenzija 2 x 0,6 cm.*

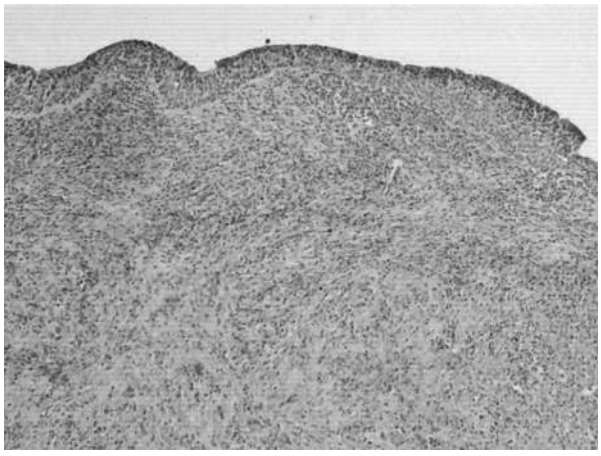

Figure 3. Photomicrograph of a mucosa with hyperplastic and metaplastic respiratory epithelium. In the lamina propria, there is diffuse infiltrate of plasma cells and lymphocytes among the bundles of spindle cells (HE x 50)
Slika 3. *Mikrografija mukoze sa hiperplastičnim i metaplastičnim respiratornim epitelom. U lamini propriji se nalazi difuzni infiltrat plazma ćelija i limfocita među snopovima vretenastih ćelija (HE x 50)*

The histopathological examination revealed that the surface of the tumor was partially covered by squamous epithelium and partially by respiratory epithelium. The epithelial surface showed signs of ulceration, with the bottom covered with granulocytes and fibrin. The lamina propria was replaced by a diffuse infiltrate of spindle cells arranged in short bundles in various directions. The cell nuclei appeared elongated and light, with visible cell nucleoli. Plasmacytoid and lymphocytoid cells were interspersed between the bundles of cells, while blood vessels were rare. Immunohistochemical staining revealed positivity to vimentin, smooth muscle actin (SMA), and ALK, while S100 and CKAE1/AE3 were negative. CD 68 and CD 45 showed focal positivity in single cells. These findings corresponded to an inflammatory myofibroblastic tumor **(Figures 3, 4 and 5).**

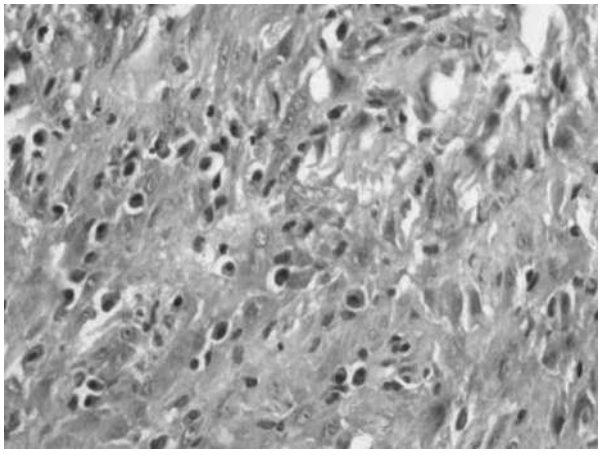

Figure 4. Detail of the tissue with plasma cells, lymphocytic cells, and numerous spindle myofibroblastic cells (HE x 400)
Slika 4. *Detalj tkiva sa plazma ćelijama, limfocitnim ćelijama i brojnim vretenastim miofibroblastičnim ćelijama (HE x 400)*

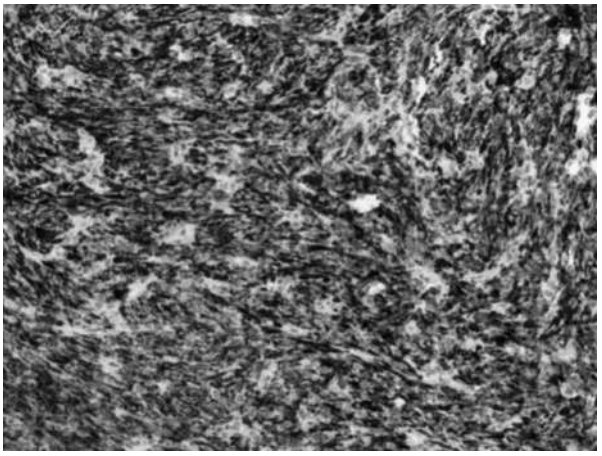

Figure 5. Immunohistochemical stain positive for expression of myofibroblastic cells of anaplastic lymphoma kinase ALK-1 protein (ALK x 200)
Slika 5. *Imunohistohemijsko bojenje pozitivno na ekspresiju miofibroblastičnih ćelija ALK-1 proteina anaplastične limfom kinaze (ALK x 200)*

Two weeks later, a follow-up tracheobronchoscopy revealed the presence of residual tumor attached to the site of the previously removed tumor in the trachea. It was observed to protrude above the surrounding smooth mucosa and was covered with blood. Subsequently, cauterization of the tumor remnant and its insertion site was performed. The next control tracheobronchoscopy was performed one month after the initial removal of the tumor and revealed the presence of scar tissue in the trachea at the site where the tumor had been removed previously. The final control tracheobronchoscopy was performed three months later, which showed no visible tumor recurrence.

Subsequently, the boy experienced periodic mild asthma exacerbations and symptoms of allergic rhinoconjunctivitis. The asthma preventive therapy was discontinued at the age of 8 years. Regular follow-up appointments with a pulmonologist were maintained, with the most recent pulmonary function checkup conducted at the age of 10. The boy remained asymptomatic, and his spirometry and body plethysmography results were within normal limits, as was his chest X-ray.

Discussion

Inflammatory myofibroblastic tumors (IMTs) were initially identified as primary lung tumors in 1939, and lung localization remains the most prevalent. However, IMTs can affect various organ systems, including the central nervous system, pelvic organs, retroperitoneum, gastrointestinal tract, orbit, and thyreoid gland [1–5]. According to the avail-

able data, IMTs account for 0.04% to 1.2% of all lung tumors, irrespective of age and sex [8]. IMTs are predominantly found in the lung parenchyma, with endobronchial tree localization accounting for approximately 5% of cases. However, its presence in the trachea is extremely rare, reported in only 2.7% of cases [3, 6–9]. In the case of our patient, the tumor was localized in the lower third of the trachea, on its lateral wall.

Traditionally viewed as reactive inflammatory lesions, IMTs are now classified as mesenchymal neoplasms of intermediate malignancy, as per the World Health Organization's 2013 classification. Their biological characteristics range from benign, locally aggressive, and recurrent forms to intermediate, potentially malignant lesions. Metastases are rare, occurring in less than 5% of cases [1, 5, 9]. Additionally, there have been reports of slow progression towards sarcoma [11]. Based on the findings from endoscopic evaluation of the respiratory tract in our patient, which did not show infiltration into surrounding structures, and the absence of recurrence in subsequent control bronchoscopies, it can be concluded that the inflammatory myofibroblastic tumor in this case exhibited a benign behavior.

The pathogenesis of IMTs remains uncertain. Several hypotheses suggest that IMTs may be associated with autoimmune or infectious mechanisms. It has been reported that in 30% of patients, IMTs have been linked to recurrent infections caused by Mycoplasma, Nocardia, Actinomycetes, and the Epstein–Barr virus. Other potential risk factors mentioned in the literature include corticosteroid use, surgery, trauma, or radiotherapy [3, 6–8]. In the case of our patient, the only identified risk factor was long-term use of inhaled steroids (budesonide) due to repeated bronchial obstruction prior to the diagnosis of IMT. Other risk factors were not present.

The activation of the immune system can cause genetic changes, and rearrangement in the ALK gene is the most common one. This gene is localized on the chromosome locus 2p23 and has been reported in 50 to 70% of cases. The activity of ALK kinase has been associated with apoptosis and has also been demonstrated in other tumors, such as small cell carcinoma of the lung and neuroblastoma [3, 7, 9]. Although some studies have shown better prognosis in tumors with ALK expression, the correlation between ALK expression and prognosis or risk of tumor recurrence is not clearly defined [3]. Other studies have found no difference in survival rates between ALK-positive and ALK-negative cases [1]. Some ALK-negative tumors are associated with ROS1 gen rearrangement. Recent studies have confirmed ETV6-NTRK3 fusion in ALK-negative pulmonary IMTs [3]. Activity of periostin, vimentin, desmin, SMA, CD 34, and S 100 are also noted [6–9]. In the case of our patient, immunohistochemical findings showed that the tumor was positive to vimentin, SMA, and ALK, and negative to S100 and CKAE1/AE3, while CD 68 and CD 45 showed focal positivity in single cells.

The diagnosis of IMT relies on the clinical presentation, laboratory and radiologic findings, endoscopic evaluation of the respiratory tract, and on histopathological verification [10–12]. The clinical presentation can vary widely, ranging from asymptomatic cases to those with severe respiratory symptoms, depending on the site of the primary tumor involvement. Some patients may also exhibit systemic manifestations such as fever, night sweats, or weight loss, often attributed to cytokine secretions [10–13]. Our patient exhibited persistent wheezing unresponsive to bronchodilator inhalation, and severe repeated bronchial obstructions requiring hospitalization. Laboratory abnormalities are uncommon, but when present, they may include findings such as anemia, thrombocytosis, elevated erythrocyte sedimentation rate, or hypergammaglobulinemia [3]. In the case of our patient, leukocytosis and thrombocytosis were observed, while other laboratory parameters were within normal limits. Radiological findings are non-specific, but imaging modalities such as chest X-ray or chest computed tomography can aid in determining the localization of the tumor [11, 12]. In the case of our patient, the chest X-ray revealed right perihilar inhomogeneous patchy infiltrates.

In children with persistent wheezing that is unresponsive to therapy, bronchoscopy evaluation is indicated to investigate potential causes of tracheobronchial obstruction. This evaluation aims to identify conditions such as foreign body aspiration, tracheal compression due to an anomalous blood vessel or other causes of tracheobronchial obstruction [12, 14]. In the case of our patient, who presented with persistent wheezing, bronchoscopy revealed intraluminal obstruction of the intrathoracic part of the trachea.

The final diagnosis of IMT is confirmed through histopathological findings [9–12]. The IMT typically consists of differentiated myofibroblasts and an inflammatory infiltrate, which includes plasma cells, lymphocytes, histiocytes, and eosinophilic granulocytes. Histologic patterns can vary, and different patterns may be observed in the same tumor [3, 6]. There are three histological subtypes of IMT: 1) the inflammatory subtype, which is characterized by a high concentration of mucus and inflammatory mediators; 2) the cellular subtype, primarily consisting of spindle myofibroblasts and inflammatory cells; and 3) the mixed type, with the predomination of collagen fibers [3,6]. In the case of our patient, the histopathological finding showed that the tumor's lamina propria was replaced by a diffuse infiltrate of spindle cells arranged in short bundles in various directions. Plasmacytoid and lymphocytoid cells were interspersed between the bundles of cells. These findings are consistent with the cellular subtype of IMT.

Macroscopically, IMTs typically present as lobular or multimodal lesions with a hard or rubbery consistency. These tumors predominantly appear as solitary lesions with dimensions ranging from 2 to 20 cm. Mul-

tiple nodular lesions are described in about one-third of cases [3]. In the case of our patient, the tumor was solitary, pale yellow in color, and possessed a firmer consistency. Its dimensions were measured at 2 x 0.6 cm.

In considering the differential diagnosis, several conditions should be taken into account. In cases of inflammatory leiomyosarcoma, cell nuclei are cigar shaped and arranged in regular fascicular patterns, while Reed Sternberg cells are observed in Hodgkin's lymphoma. Inflammatory fibroid polyps primarily manifest in the gastrointestinal tract. Imunoglobulin (Ig) G4 sclerosing disease typically affects older individuals. While some studies have reported the presence of IgG4-positive cells in IMTs, the extent of positivity of these cells and the IgG4/IgG ratio are typically lower compared to IgG4-related diseases [3].

The gold standard for the treatment of IMTs is complete resection of the tumor, either through interventional bronchoscopy or open lung surgery [13, 15, 16]. In our patient's case, bronchoscopic extraction of the tumor was successfully performed, along with cauterization of the tumor remnant and its insertion site during the control bronchoscopy.

Unresectable lesions require adjuvant therapies with chemotherapy, radiation therapy, COX-2 inhibitors, and steroids [13, 15, 17]. Corticosteroids have demonstrated efficacy in the treatment of some cases of unresectable lesions, although long-term use may lead to rapid proliferation of airway fibroblasts and tumor progression, possibly due to immunosuppression [18]. Celocoxib (a COX-2 inhibitor) and bronchoscopic argon plasma coagulation have emerged as treatment alternatives in recent years [17].

The discovery of ALK rearrangements has paved the way for targeted therapy with ALK inhibitors, with crizotinib being the most commonly used agent. Like most tyrosine kinase inhibitors, crizotinib acts on a wider scale than the target gene, inhibiting not only ALK but also ROS 1, and MET, which explains the positive treatment response in some ALK-negative tumors [13, 15, 16].

The prognosis is favorable following complete excision of the tumor. The five-year survival rate is approximately 90%, and the ten-year survival rate is nearly 70%. As local recurrences occur in 5 to 25% of patients, radiographic and bronchoscopic monitoring is recommended after the initial surgical treatment, as it was done in the case of our patient [8, 11–13].

Conclusion

Tracheal inflammatory myofibroblastic tumors are very rare neoplasms in children, with a borderline risk of malignancy. They can present with symptoms similar to the most prevalent respiratory illnesses, making diagnosis challenging. Therefore, bronchoscopy should be performed in persisting respiratory diseases, particularly wheezing, which do not improve with standard treatment.

The gold standard in the treatment of these tumors is radical surgery, while chemotherapy and radiotherapy may be considered for unresectable lesions, or recurrent tumors. Targeted therapy may be an option for the treatment of anaplastic lymphoma kinase positive inflammatory myofibroblastic tumors. Addressing the challenges associated with identifying new genetic rearrangements, refining therapies and application methods, as well as optimizing therapy duration represent key priorities to improved management and outcomes for affected patients.

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Case report
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ENDOVASCULAR TREATMENT OF VISCERAL ARTERY ANEURYSMS − CASE REPORTS

ENDOVASKULARNI TRETMAN ANEURIZME VISCERALNIH ARTERIJA − PRIKAZ SLUČAJEVA

Nikola BATINIĆ[1, 2], Vladimir MANOJLOVIĆ[1, 2], Dragan NIKOLIĆ[1, 3], Andrej PETREŠ[4] and Katarina PETROVIĆ[2]

Summary

Introduction. Visceral artery aneurysms, including those affecting the splenic and hepatic arteries, rank among the most common types of abnormalities within the visceral arterial system. Treatment options for visceral artery aneurysms include open surgery and endovascular repair, with the latter being preferred for anatomically suitable and asymptomatic patients. **Case Report.** We present two cases, where the first concerns a 72-year-old male patient with an asymptomatic large common hepatic artery aneurism measuring 4.5 cm in maximum diameter. Computed tomography angiography revealed a 1.1 cm enlargement of the aneurism maximum diameter over a two-year period. The second case involves a 65-year-old female patient with asymptomatic splenic artery aneurism measuring 3.2 cm in maximum diameter. Both patients underwent endovascular stent deployment as part of their treatment regimen. No complications were observed during the early and late post-procedural phases. Follow-up imaging via control computed tomography angiography one month after the procedure revealed transparent stents in both cases without evidence of endoleaks. **Conclusion.** Endovascular stent deployment emerges as a safe and most efficient treatment modality for asymptomatic visceral artery aneurysms

Key words: Endovascular Aneurysm Repair; Splenic Artery; Hepatic Artery; Aneurysm; Computed Tomography Angiography; Treatment Outcome

Sažetak

Uvod. Aneurizma lijenalne arterije i aneurizma hepatične arterije su najčešće aneurizme visceralnih arterija. Aneurizme visceralnih arterija mogu biti zbrinute otvoreno hirurški ili endovaskularno. Endovaskularni tretman je prvi izbor kod anatomski pogodnih i asimptomatskih pacijenata. **Prikaz slučaja.** Prikaz slučaja dva pacijenta. Prvi pacijent je 72 godine star muškarac sa asimptomatskom velikom aneurizmom zajedničke hepatične arterije sa maksimalnim prečnikom od 4,5 cm. Kompjuterizovana tomografska angiografija pokazala je uvećanje maksimalnog prečnika od 1,1 cm za dve godine. Drugi pacijent je 65 godina stara žena sa asimptomatskom aneurizmom lijenalne arterije maksimalnog prečnika 3,2 cm. Oba pacijenta su tretirana endovaskularnom *stent deployment* metodom. Rani i kasni postproceduralni tok je protekao uredno bez komplikacija. Kontrolna angiografija kompjuterizovanom tomografijom urađena je jedan mesec nakon procedure i u oba slučaja je prikazala stent koji je prohodan i bez endolika. **Zaključak.** Endovaskularno rešavanje aneurizmatske bolesti uz simultanu endovaskularnu restituciju arterijskog protoka u arteriji je bezbedna metoda i predstavlja najbolji način lečenja asimptomatskih aneurizmi visceralnih arterija.

Ključne reči: endovaskularni tretman aneurizme; lijenalna arterija; hepatična arterija; aneurizma; CT angiografija; ishod lečenja

Introduction

An aneurysm is a permanent, concentric or eccentric, segmental dilatation in the wall of an artery, measuring at least 1.5 times its normal diameter [1, 2]. Aneurysms affecting the visceral arteries are rare but clinically significant vascular condition. Splenic artery aneurysm (SAA) and hepatic artery aneurysm (HAA) are the most common types of visceral artery aneurysms [3, 4]. Rupture, the most severe complication, is associated with a high mortality rate [5, 6]. Computed tomography angiography (CTA) serves as the gold standard in diagnostics [5−7]. Treatment options for visceral artery aneurysms include open surgery and endovascular repair, with the latter being the preferred choice in anatomically suitable and asymptomatic patients.

The aim of this study is to present two cases of large HAA and SAA successfully treated using the endovascular stent deployment method.

Case Report

The first case involves a 72-year-old male who, two years prior, underwent a CT scan following an abdominal injury sustained in a traffic accident. This scan, conducted as part of emergency diagnostics, revealed HAA with a maximum diameter of 3.4 cm.

Two years later, the patient presented to a vascular surgeon. Despite being completely asymptomatic, he had a medical history significant for hypertension, long-term smoking, chronic gastritis, and a past COVID infection three years prior. A subsequent CTA revealed large aneurysm of the common hepatic ar-

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Abbreviations

SAA – Splenic artery aneurysm
HAA – Hepatic artery aneurysm
CTA – Computed tomography angiography
DUS – Duplex ultrasound

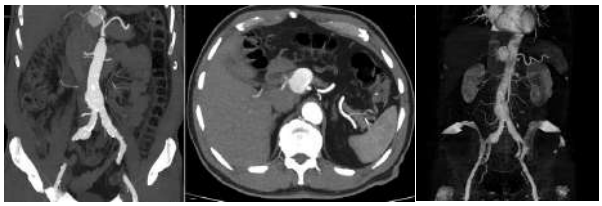

Figure 1. CTA revealing enlargement of the hepatic artery aneurysm, abdominal aortic aneurysm and aneurysm of right common iliac artery
Slika 1. *Kompjuterizovana tomografska angiografija na kojoj je opisano uvećanje aneurizme hepatične arterije, aneurizma abdominalne aorte i aneurizma desne zajedničke ilijačne arterije*

tery, with maximum diameter of 4.5 cm, an abdominal aortic aneurysm measuring 4 cm in diameter, and an aneurysm of right common iliac artery with maximum diameter of 2.3 cm **(Figure 1).** CTA indicated an increase in the maximum diameter of the HAA by 1.1 cm over the course of two years.

Considering the patient's completely asymptomatic status alongside the significant enlargement of the large HAA, we opted for an endovascular stent deployment procedure, in accordance with the established guidelines.

The procedure was performed in the angiography room in the Radiology Center of the University Clinical Center of Vojvodina, with collaboration from a vascular surgeon, interventional radiologist, and anesthesiologist. Brachial artery puncture was conducted under ultrasound guidance. A non-selective angiography of the abdominal aorta was initially performed, followed by a selective angiography of the celiac trunk. Confirmation of a large aneurysm of the common hepatic artery was obtained, and a Jotec 5x38 mm stent graft was subsequently placed. Control angiography revealed normal findings, without evidence of endoleaks or residual filling of the aneurysm, and preserved flow of the branches **(Figure 2).** The procedure

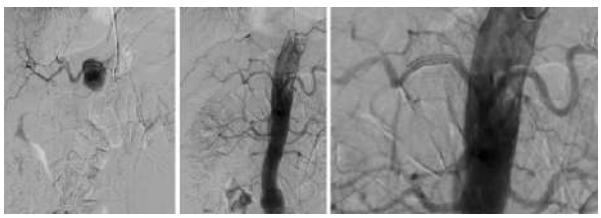

Figure 2. Selective angiography of the celiac trunk, and stent deployment in the common hepatic artery aneurism. Follow-up angiography without evidence of endoleaks
Slika 2. *Selektivna angiografija celijačnog trunkusa i postavljanje stenta u aneurizmu zajedničke hepatične arterije. Kontrolna angiografija bez endolika*

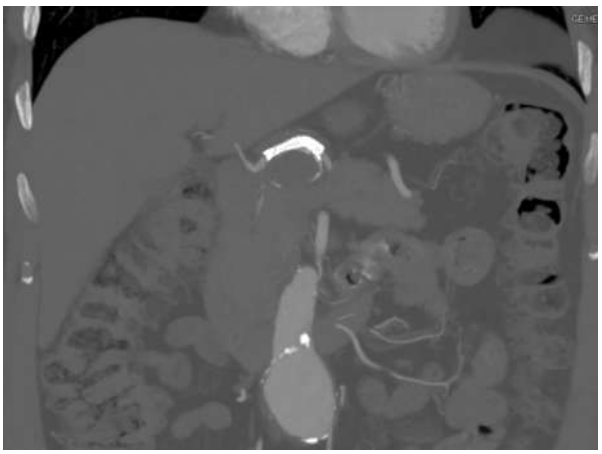

Figure 3. Follow-up CTA after endovascular treatment of the hepatic artery aneurysm, without evidence of endoleaks
Slika 3. *Kontrolna kompjuterizovana tomografska angiografija nakon endovaskularnog tretmana aneurizme hepatične arterije, bez endolika*

transpired without complications, with the administration of 5000 IU of Heparin during the intervention.

The post-procedural recovery progressed smoothly, and the patient was discharged the following day for home care, with a prescription of dual antiplatelet therapy. In the early stage, on the third day post-endovascular procedure, a small hematoma developed in the site of the brachial artery puncture, which was effectively managed through conservative measures.

One month post-procedure, a follow-up CTA was conducted, revealing patent stent without evidence of endoleaks and preserved flow in the branches, indicative of normal findings **(Figure 3).**

The second case involves a 65-year-old female patient diagnosed with an aneurysm of the splenic artery, as identified on CTA. The maximum diameter of the aneurysm measured 3.2 cm, lacking clear demarcation of the neck and thrombotic masses, with a partially calcified wall **(Figure 4).** The patient remained asymptomatic but presented with hypertension, cardiomyopathy, hypothyreoidism, hepatic steatosis, and psoriasis.

Given the patient's asymptomatic status and the presence of a large SAA, a decision was made to proceed with an endovascular stent deployment procedure.

The procedure was performed similarly to the previous one, with a brachial artery puncture guided by

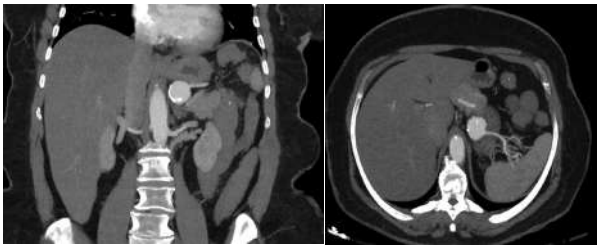

Figure 4. CTA revealing splenic artery aneurysm
Slika 4. *Kompjuterizovana tomografska angiografija na kojoj je prikazana aneurizma lijenalne arterije*

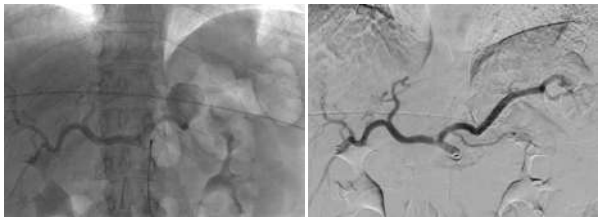

Figure 5. Selective angiography of the splenic artery and celiac trunk, and stent deployment in the splenic artery aneurism. Follow-up angiography without evidence of endoleaks
Slika 5. *Selektivna angiografija lijenalne arterije i celijačnog trunkusa i postavljanje stenta u aneurizmu lijenalne arterije. Kontrolna angiografija bez endolika*

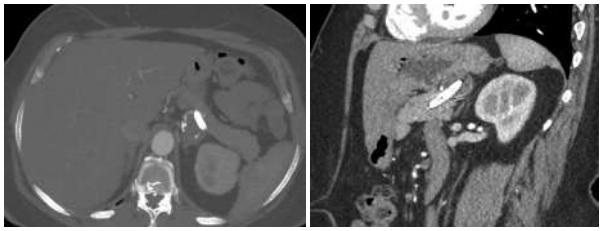

Figure 6. Follow-up CTA without endoleaks
Slika 6. *Kontrolna kompjuterizovana tomografska angiografija bez endolika*

ultrasound. Initially, a non-selective angiography of the abdominal aorta was performed, followed by a selective angiography of the celiac trunk. Subsequently, a large splenic artery aneurism was confirmed, and a Jotec 5x37 mm stent graft was deployed. Control angiography revealed normal findings without evidence of endoleaks or residual aneurism filling **(Figure 5).** During the procedure, 4000 IU of Heparin was administered.

The patient's early and late post-procedural course progressed without complications, and the patient was discharged the next day for home case, with dual antiplatelet therapy prescribed. A follow-up CTA performed one month later indicated a transparent stent without evidence of endoleaks **(Figure 6).**

Discussion

Visceral artery aneurysms are rare, but the complications are often life-threatening [4, 8]. The precise etiology of HAA and SAA remains unclear, though atherosclerosis is commonly implicated, while hypertension is a frequent comorbidity as per literature. Additionally, liver cirrhosis, portal hypertension, female gender, and pregnancy are identified as major risk factors for visceral artery aneurysms [4].

Guidelines recommend repair for HAA exceeding 2 cm in diameter and SAA exceeding 3 cm in diameter, as well as for all symptomatic aneurysms, pregnant women, and instances where the aneurysm enlarges by over 0.5 cm per year [4, 9, 10]. However, some studies have not established a clear correlation between the aneurism diameter and the risk of rupture [11].

Rupture of a visceral artery aneurysm, the most severe complication, posed a life-threatening situation often presenting as hemorrhagic shock, necessitating urgent surgical intervention. HAA rupture can sometimes lead to biliary tract involvement, manifesting as Quincke's triad, which includes jaundice, biliary colic and gastrointestinal bleeding [12]. Most visceral aneurysms are diagnosed only after rupture occurs [13]. Treating ruptured HAA can be more challenging due to the complexity of maintaining hepatobiliary system perfusion [14].

With the development of sophisticated imaging modalities such as CTA, magnetic resonance angiography, and duplex ultrasound (DUS), the diagnosis of visceral artery aneurysms in asymptomatic stages has become more accessible, leading to improved treatment outcomes [4, 5]. While DUS is a safe diagnostic tool, it has its limitations. Its sensitivity in detecting SAA and HAA smaller than 3 cm is poor, and it may be hindered by bowel gas shadowing and obesity [4]. Therefore, we opted for CTA for precise measurement, assessment of aneurysm enlargement, consideration of endovascular treatment feasibility, and post-procedural follow-up.

The primary goal in treating visceral artery aneurisms is early detection and intervention in the asymptomatic stage. Ideally, the chosen procedure should exclude the aneurysm while preserving circulation, achievable through stent graft placement and endovascular exclusion [4]. Both our cases involved completely asymptomatic patients: one with a large HAA that enlarged by 1.1 cm over 2 years, and the other with an SAA with a maximum diameter of 3.2 cm. Considering anatomical characteristics, maximum diameter, aneurysm enlargement, location, and asymptomatic presentation, we opted for stent deployment to maintain blood flow through the affected artery. Coil embolization is the preferred choice for complex aneurysms, where stent graft placement is not feasible, or ruptured aneurisms in hemodynamically unstable patients.

Open surgical treatment remains a viable option for visceral artery aneurysms. There are several case series or individual cases found in literature that demonstrate successful outcomes with open surgical treatment [3, 5]. In most cases, open surgical treatment was conducted in ruptured or symptomatic aneurysms. However, due to its minimally invasive nature, advanced techniques, and relatively low morbidity rated, endovascular treatment is preferred for both asymptomatic and symptomatic aneurysms in anatomically suitable patients.

Complications after-endovascular treatment are generally rare or minimal, as observed in our first case, making it a favorable option over open surgery.

Conclusion

Visceral artery aneurysms represent a rare yet perilous condition. The primary objective is the early detection and treatment of these conditions, preferably in the early asymptomatic stage. Endovascular stent deployment emerges as a safe and optimal therapeutic approach for managing asymptomatic visceral artery aneurysms.

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Case report
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INADEQUATE DIETARY INTAKE AND PEDICULOSIS AS THE UNDERLYING CAUSE OF IRON DEFICIENCY ANEMIA – CASE REPORT

NEADEKVATAN UNOS HRANE I PEDIKULOZA U OSNOVI ANEMIJE UZROKOVANE NEDOSTATKOM GVOŽĐA − PRIKAZ SLUČAJA

Milica ZIROJEVIĆ[1, 2], Božidar DEJANOVIĆ[1, 3], Željka SAVIĆ[1, 3], Sonja SEDLAREVIĆ[1, 2], Dušan GRUJIĆ[1, 4] and Kristina STEPANOVIĆ[1, 2]

Summary

Introduction. Causes of iron deficiency anemia include inadequate dietary intake, increased body requirements, reduced iron absorption, chronic inflammation, and chronic blood loss. Individuals residing in socioeconomically disadvantaged areas are prone to iron deficiency, primarily due to inadequate dietary intake, with parasitic infestations being a rare cause. Pediculosis, caused by *Pediculus humanus capitis,* is an ectoparasitic infestation of the human scalp. **Case Report.** We present the case of a 52-year-old Caucasian female who sought emergency medical attention due to progressive fatigue and pallor. The patient denied any history of gastrointestinal or genitourinary bleeding. Nutritional assessment revealed an inadequately balanced diet with a suspected deficiency of iron-rich foods. Physical examination was unremarkable, except for decreased muscle mass. A pronounced infestation with lice along with a large number of nits was observed on the head. Laboratory tests confirmed severe sideropenic anemia. Endoscopic, radiological and specific laboratory examinations failed to provide significant information about the etiology of the anemia. Initially, the patient received transfusions of deplasmatized erythrocytes, followed by oral ferrous sulfate preparations, which resulted in satisfactory substitution. Topical application of Permethrin 1% lotion was administered, followed by the use of a lice comb. **Conclusion.** This case underscores the significance of a comprehensive approach to patients with chronic head and body lice infestation, including basic laboratory analyses and an iron profile, if necessary. Many patients receive over-the-counter therapy without an adequate hematological assessment. Only through this approach can hematological disorders associated with chronic or recurrent pediculosis be promptly diagnosed and treated, thus preventing the potentially fatal complications of anemia.

Key words: Anemia, Iron-Deficiency; Diet; Iron Deficiencies; Lice Infestations; Socioeconomic Factors

Sažetak

Uvod. Uzroci anemije usled nedostatka gvožđa obuhvataju neadekvatan unos hrane, povećane telesne potrebe, smanjenu apsorpciju gvožđa, hroničnu inflamaciju i hronični gubitak krvi. Osobe iz socijalno ekonomski ugroženih sredina podložne su razvoju deficita gvožđa, pretežno zbog neizbalansirane ishrane, ređe i zbog parazitarnih infestacija. Pedikuloza je ektoparazitska infestacija poglavine izazvana vrstom *Pediculus humanus capitis.* **Prikaz slučaja.** Predstavljamo bolesnicu starosti 52 godine, svetle puti, koja je zatražila hitnu medicinsku pomoć zbog progresivnog umora i bledila. Bolesnica negira istoriju gastrointestinalnog ili genitourinarnog krvarenja. Nutritivna procena otkrila je neadekvatno balansiranu ishranu sa mogućim nedostatkom unosa namirnica bogatih gvožđem. Fizikalni pregled bio je bez značajnih osobenosti, osim smanjenja mišićne mase. Na poglavini je uočena izražena infestacija vašima i velikim brojem jajašaca. Laboratorijski testovi su potvrdili izraženu sideropenijsku anemiju. Endoskopski, radiološki i specifični laboratorijski pregledi nisu pružili značajne informacije o etiologiji malokrvnosti. Bolesnici su inicijalno ordinirane transfuzije deplazmatisanih eritrocita, potom i oralni preparati gvožđe-sulfata, što je dovelo do zadovoljavajuće supstitucije. Lokalno je primenjen permetrin u vidu losiona od 1%, uz upotrebu češlja za vaši. **Zaključak.** Ovim slučajem ističemo važnost sveobuhvatnog pristupa bolesnicima sa hroničnom infestacijom vašima na glavi i telu, uključujući osnovne laboratorijske analize i, ako je potrebno, analize metabolizma gvožđa. **Mnogim bolesnicima se propisuje terapija bez recepta, bez adekvatne hematološke procene. Samo ovim pristupom mogu se dijagnostikovati i lečiti hematološki poremećaji u vezi sa hroničnom ili ponavljanom pedikulozom, sprečavajući potencijalno smrtonosne komplikacije anemije.**

Ključne reči: anemija uzrokovana deficitom gvožđa; ishrana; deficit gvožđa; pedikuloza; socioekonomski faktori

Introduction

Sideropenic anemia is a hypochromic, microcytic anemia caused by insufficient iron level in the body. Globally, anemia affects approximately 33% of the world's population, encompassing about 1.62 billion individuals, with nearly half of the cases attributed to iron deficiency, thus constituting a sub-

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Abbreviations
IgA – immunoglobulin A

stantial disease burden worldwide [1–3]. Causes of iron deficiency anemia include inadequate dietary intake, increased body requirements, reduced iron absorption, chronic inflammation, and chronic blood loss [4, 5]. Individuals residing in socioeconomically disadvantaged areas are particularly vulnerable to iron deficiency, primarily due to inadequate dietary intake and rarely due to parasitic infestations [6, 7]. Pediculosis, caused by *Pediculus humanus capitis,* is an ectoparasitic infestation of the human scalp and it is highly contagious, commonly transmitted through direct head-to-head contact with an infected individual. Indirect transmission through the sharing of personal items is less frequent. The prevalence of pediculosis varies depending on socioeconomic, demographic, educational and hygiene factors [8–10]. The parasite sustains itself by feeding on human blood, with estimated blood loss ranging from 0.008 ml/day to 0.7 ml/day in severe infections. Each milliliter of blood contains 0.4–0.5 mg of iron. In certain cases, the cumulative blood loss over time can precipitate symptoms of anemia in affected individuals [11, 12].

Case Report

A 52-year-old Caucasian female presented to the emergency department in May 2023 complaining of progressive fatigue and pallor. The patient denied any history of gastrointestinal or genitourinary bleeding, as well as any change in bowel (diarrhea, constipation) or urine (dysuria, frequency, urgency) habits. Prior to hospitalization, she had not sought medical attention for over 20 years and had not been taking any medications. She reported regular menstrual cycles without overflow or any signs of menorrhagia until 12 months before her hospital admission, when menopause began. Nutritional assessment revealed imbalanced meals with suspected inadequate consumption of iron-rich foods.

Upon initial examination, her skin appeared notably pale, and she exhibited a significant infestation of head lice with numerous nits on the scalp. Vital signs were within normal limits. Systemic examination revealed no abnormalities except for muscle wasting and low fat stores. Her body mass index was 15.6 kg/m^2. There was no lice infestation on the rest of her body or pubic region, aside from the head.

Laboratory tests confirmed profound microcytic anemia, with white blood cells count, platelets, markers of inflammation, parameters of hemostasis, electrolytes, renal and liver functional tests all falling within normal ranges **(Table 1).** The iron profile indicated low iron and ferritin levels, as along with markedly elevated soluble transferrin receptor, which confirmed the diagnosis of iron deficiency anemia **(Table 2).** Fecal occult blood test was negative.

Following a local diagnostic protocol for evaluation patients with sideropenic anemia, upper and lower endoscopies were conducted, revealing no significant pathomorphological abnormalities in the esophageal, gastric, duodenal or colonic mucosa. Pathohistological analysis of gastric and duodenal mucosal biopsies did not indicate signs of *Helicobacter pylori* infection,

Table 1. Baseline laboratory parameters of the patient with iron deficiency anemia
Tabela 1. *Inicijalne laboratorijske vrednosti bolesnice sa sideropenijskom anemijom*

	Baseline value/*Osnovna vrednost*	Normal range/*Normalan opseg*
RBC x 10^{12}/L/*ERCI x* 10^{12}*/L*	2.1	4.2-6.0
Hemoglobin g/L/*Hemoglobin g/L*	31.0	120-160
MCV FL	62.5	82-98
MCH pg	22.4	27-32
MCHC g/L	293	310-350
WBC x 10^9/L/*LKCI x* 10^9*/L*	5.54	4.0-10.0
PLT x 10^9/L/*TRCI x* 10^9*/L*	240	140-40
Urea mmol/L/*Urea mmol/L*	5.5	2.2-7.1
Creatinine µmol/L/*Kreatinin*	53	49-97
AST U/L	12	5-37
ALT U/L	16	5-48
Total Bilirubin umol/L/*Ukupni bilirubin*	5.5	3-21
Direct Bilirubin umol/L/*Direktni bilirubin*	2.0	0,1-5,2
Na mmol/L	139	135-148
K mmol/L	4,3	3.5-5.5
Cl mmol/L	104	98-112
CRP mg/L/*CRP mg/L*	0.5	0.0-5.0

Legend: RBC – Red Blood Cells, MCV – Mean Corpuscular Volume, MCH – Mean Corpuscular Hemoglobin, MCHC – Mean Corpuscular Hemoglobin Concentration, WBC –White Blood Cells, PLT – Platelets, AST – Aspartate Aminotransferase, ALT – Alanine Transaminase, Na – Sodium, K – Potassium, Cl – Chloride, CRP – C-reactive protein
Legenda: ERCI – eritrociti, MCV – prosečna zapremina eritrocita, MCH – prosečna količina hemoglobina u eritrocitu, MCHC – prosečna koncentracija hemoglobina u eritrocitima, LKCI – leukociti, TRCI – trombociti, AST – aspartat aminotransferaza, ALT – alanin aminotransferaza, Na – natrijum, K – kalijum, Cl – hlor, CRP – C-reaktivni protein

Table 2. Iron profile of the patient with iron deficiency anemia
Tabela 2. *Profil gvožđa kod bolesnice sa sideropenijskom anemijom*

	Baseline value/*Osnovna vrednost*	Normal range/*Normalan opseg*
Ferritin/*Feritin* ug/L	6.0	10-120
Transferrin/*Transferin* g/L	3.52	1.8-3.6
Fe/*Gvožđe* umol/L	5.0	9.0-30.4
sTfR mg/L	15.4	0.76-1.76

Legend: Fe – Mean iron, sTfR – Mean Soluble Transferrin Receptor
Legenda: Fe – Gvožđe, sTfR – Solubilni transferinski receptori

atrophic gastritis, or celiac disease. Serological tests for immunoglobulin A (IgA), anti-tissue transglutaminase and IgA anti-endomysial were negative, with total IgA falling within normal range values. Thyreoid function tests also fell within normal range **(Table 2).** Pelvic ultrasound, performed by the gynecologist, and a computed tomography examination conducted according to the chest-abdomen-pelvis protocol did not reveal any significant findings considering the etiology of sideropenic anemia.

The patient initially received several units of packed red blood cells, leading to subsequent normalization of hemoglobin levels. Oral ferrous sulfate was then administrated. Following a dermatology consultation, permethrin 1% lotion was applied to the hair and scalp, followed by the use of a nit comb. The patient was advised to repeat the treatment one week later.

Discussion

In men, as well as in postmenopausal women, iron deficiency anemia typically arises from either gastrointestinal iron loss or decreased iron absorption in the gastrointestinal tract [13]. Here, we present a case of severe sideropenic anemia induced by recurrent *Pediculosis capitis* infestation and arguably inadequate dietary intake. Although inadequate dietary intake is a well-known cause of iron deficiency anemia, it is infrequent in developed countries but quite common in developing ones. Hematologic disorders as complications of pediculosis are rarely recognized [14–16]. The population at high risk for sideropenic anemia in the context of pediculosis includes children, individuals with a history of psychiatric disorders, poor education, and low socioeconomic status [9]. The patient in question exhibited multiple precipitating factors, including low socioeconomic status, limited education, and poor personal hygiene, rendering her susceptible to profound iron deficiency and subsequent iron deficiency anemia. Despite extensive history-taking, laboratory, endoscopic and radiological investigations, no obvious underlying condition was identified to explain the anemia, aside from chronic and heavy lice infestation.

Conclusion

This case underscores the significance of adequate approach to patients with chronic head and body lice infestation, including, at least, basic blood work and an iron profile, if necessary, as most of them are simply provided with over-the-counter or prescription anti-lice medications by healthcare providers. It is imperative to adopt a comprehensive approach to diagnose and treat hematologic disorders associated with recurrent pediculosis promptly, which is crucial for averting potentially life-threatening complications arising from anemia.

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EDITORIAL ANNOUNCEMENTS
SAOPŠTENJA UREDNIŠTVA

THE PIONEERS OF NEUROPSYCHIATRY – THERE IS NO FUTURE WITHOUT THE PAST

On the occasion of the 20th anniversary of passing away and the 118th anniversary of birth of Professor Doctor Nemanja Vurdelja (Ličko Petrovo Selo, June 6, 1906 – Novi Sad, May 25, 2004)

We commemorate him as one of the foremost professors and founders of the School of Medicine in Novi Sad, the luminary and founder of the Clinic of Neuropsychiatry in Novi Sad, a dedicated participant in the meetings of the members of the Novi Sad branch of the Association of Physicians of Vojvodina, a long-standing member and president of the Editorial Board of the Medical Review. He was a laureate of numerous prestigious professional, scientific, and social awards, including Annual Awards for Scientific and Research Work from the Association of Physicians of Vojvodina, the October Award of Novi Sad, the Gold Badge of the Red Cross of Yugoslavia, the title of Honorary President of the Association of Neurologists and the Association of Psychiatrists of Yugoslavia, the Lifetime Achievement Award from the Association of Physicians of Vojvodina – Serbian Medical Association. He was an Honorary Member of the Association of Teachers and Scientific Workers of Serbia, and was bestowed the title of Honorary Doctor by Novi Sad University.

In everlasting memory of this remarkable individual – a teacher to numerous generations of medical students and neurology and psychiatry specialists, a pinnacle of professional excellence in Vojvodina medicine, a devoted public educator, and a legendary figure of Novi Sad - his legacy was commemorated on June 6, 2017, the 111th anniversary of his birth. On this occasion, his bust was unveiled in the hall of the Institute within the current Clinic for Neurology and Psychiatry of the Clinical Center of Vojvodina.

(The sculptor and donor of the sculpture is Dr. Vladimir T. Jokanović, a distinguished friend of Dr. Vurdelja and an esteemed academician in the field of medicine).

He taught us that true listening does not necessitate following advice blindly; that the pursuit of happiness is a long journey to reaching satisfaction; that happiness cannot be given, taken or possessed, but is rather a fleeting feeling experienced only briefly.

Despite unfavorable genetic and socio-historical circumstances of his time, he demonstrated adaptability and leveraged extensive medical knowledge to gain control over his life, actively reaching into his tenth decade.

Even in his later years, he delivered concise, articulate, and compelling lectures to academic audience. He strongly believed that fostering correct and widespread positive interpersonal relationships forms the bedrock for further progress within any social community. This required continual investment in nurturing and improving these relationships, alongside expressing gratitude for received kindness. He cherished creative work as an integral and essential aspect of daily life, inseparable from the subtle emotional dimensions of humanity, as such a life enriches one with joy and contentment. For a man engaged in work and creation, he believed that this is when everyone truly understands who he is, what he is and what he is worth. Life without work is mere existence, and an idler is a sufferer and an emotional pauper devoid of life's joys.

On his 97th birthday celebration, he delivered a legendary lecture in his apartment, standing for 45 minutes before newspaper, radio and television reporters, alongside numerous high-ranking officials from Novi Sad University and health institutions. He declared that although he possessed the will to live, his physical strength had begun to falter. He prophesied that there would be no birthday celebration the following year, stating "Death will claim me where I rightfully belong! Do not pity me – do not mourn for me at all! Where I am headed, there is no suffering – it is true that there may be no breath, but there are no sighs either...everything is uniform and equal for everyone there. Do not fear the end of life; it is not scary to die – it is scary not to live! While you are alive and able, invest all your abilities to live as contentedly as possible, as better and as more as possible, savoring joys that only life can bring. Rejoice in it and always remember the profound truth that life is incredibly beautiful and interesting – a priceless gift bestowed upon every fortunate soul!"

Assigned a symbolic birth date of 06/06/1906 by fate, he faced the end of his battle with Life in his distinctive style. Just five minutes before his passing, on 05/25 at 5:00, he called out Death, saying: "I am going to die now", then turned away from the witnesses present and embraced Eternity. On that day, the newspaper headline read, "On Youth Day in Novi Sad, the city's oldest citizen passed away." He became the first among the citizens of Novi Sad to be cremated, and the urn containing his ashes rests in the initial section of the Columbarium of the Novi Sad City Cemetery.

He was and remains vivid in the memories of many fellow citizens, patients and especially students, admirers and followers – a guiding light for generations: a conscientious and responsible doctor, a humane and honest man, a measured and wise conversationalist, a persistent and diligent scientist, a consistent and witty friend, a successful educator and captivating lecturer, eloquent and educated, serious and fair, elegant and dignified, a wizard of words and an interpreter of the eternal mysteries of the human soul, a magician of jokes, a virtuoso of speech, and a sage in finding simple solutions even in the most difficult circumstances.

Memories are a monument more enduring than stone, and an indelible one stands as the noblest tribute for future generations to honor their ancestors. His memory stands as a monument to all doctors deserving the legendary status of Doctor NEMANJA VURDELJA! As practitioners of his art, we proudly carry on his legacy – the work of a remarkable physician, lecturer, scientist, and public educator – a luminary and legend of Serbian, Vojvodina, and Yugoslav neurology and psychiatry. As admirers of Professor Vurdelja's image and work, his students and followers, we remember his with profound gratitude for his contributions to our profession. It is with utmost reverence and conviction that we uphold his memory, believing there is no greater tribute than to preserve and cherish the memories of him and his remarkable achievements.

Prof. dr Milorad Žikić

PIONIRI NEUROPSIHIJATRIJE − BEZ PROŠLOSTI NEMA NI BUDUĆNOSTI

Povodom 20. godišnjice od odlaska u večnost i 118. godišnjice rođenja profesora doktora Nemanje Vurdelje (Ličko Petrovo Selo 6. 6. 1906–Novi Sad, 25. 5. 2004)

Sećamo ga se među prvoizabranim profesorima i osnivačima Medicinskog fakulteta u Novom Sadu, korifeja i utemeljivača Klinike i Katedre za neuropsihijatriju u Novom Sadu, doslednog učesnika sastanaka članova novosadske podružnice Društva lekara Vojvodine, dugogodišnjeg člana i predsednika Redakcijskog odbora Medicinskog pregleda, laureata mnogih visokih stručnih, naučnih i društvenih priznanja: godišnje nagrade za naučnoistraživački rad Društva lekara Vojvodine, Oktobarske nagrade Novog Sada, nosioca zlatne značke Crvenog krsta Jugoslavije, zvanja počasnog predsednika Udruženja neurologa i Udruženja psihijatara Jugoslavije, nagrade za životno delo Društva lekara Vojvodine – Srpskog lekarskog društva, počasnog člana Udruženja nastavnika i naučnih radnika Srbije, počasnog doktora Univerziteta u Novom Sadu...

U znak večnog pamćenja na velikana među učiteljima brojnih generacija studenata medicine i specijalizanata neurologije i psihijatrije, stručnu gromadu vojvođanske medicine, posvećenog narodnog prosvetitelja i urbanu legendu Novog Sada, povodom 111. godišnjice rođenja 6. juna 2017. postavljena je njegova bista u holu Instituta, sadašnjih klinika za neurologiju i psihijatriju Kliničkog centra Vojvodine.

(Autor i donator skulpture je prijatelj dr Vurdelje akademik medicine prim. dr Vladimir T. Jokanović.).

Učio nas je da znati slušati ne znači da se savet mora i poslušati, da je u potrazi za srećom veliki domet dostizanje osećanja zadovoljstva, da se sreća ne može dati, uzeti ni imati, a samo retko i na kratko se može i osetiti.

Iako mu ni genetika ni društveno-istorijski period u kome je živeo nisu bili naklonjeni, adaptabilnošću i korišćenjem velikog medicinskog znanja uspostavio je kontrolu nad životom i aktivno dosegao duboko u desetu dekadu života.

I pred sam kraj života bio je sposoban da u trajanju akademskog časa održi sažeto, razgovetno i ubedljivo predavanje svakoj publici. Duboko je verovao da je korektan i opšterasprostranjen dobar međuljudski odnos temelj svakog daljeg napretka u društvenim zajednicama bilo kog formata. Takođe i da je neophodan stalni ulog u njegovom negovanju i unapređivanju, ali i izražavanje zahvalnosti za primanje dobrih dela. Voleo je stvaralački rad i smatrao ga sastavnim delom i esencijom svakodnevnog života, neodvojivog od suptilnog emotivnog života ljudi, jer čoveka samo takav život ispunjava radošću i zadovoljstvom. Za čoveka koji radi i stvara govorio je da ga onda svi znaju, i ko je, šta je i koliko vredi... da je život bez rada puko životarenje, a neradnik stradalnik i emotivni siromah, jer je osoba bez životne radosti.

Na proslavi 97. rođendana u svom stanu je održao legendarno predavanje stojeći 45 minuta pred predstavnicima novinskih, radio i televizijskih izveštača, brojnim visokim zvanicama Novosadskog univerziteta i zdravstvenih ustanova, izjavljujući da volje za životom ima ali ga izdaje fizička snaga, i proročki poručio

da rođendanske proslave naredne godine neće biti – „Smrt će me ostaviti tamo gde mi je već odavno mesto! Nemojte me žaliti, nemojte mi to nikako raditi! Tamo gde idem jada nema – istina je da tamo nema daha, ali nema ni uzdaha ... svima je tamo sve isto i jednako. Ne bojte se svršetka života, nije strašno umreti, strašno je ne živeti! Dok ste živi i dok možete uložite sve sposobnosti da ga proživite što zadovoljniji, koliko god se bolje i više može, u radostima koje samo život može da nosi. Radujte mu se i mislite uvek na istinu da je život jako lep i interesantan, da je svakom srećniku koji ga je dobio neuporedivo najlepši dar!“

Kao što mu je sudbinski bio određen simbolični datum rođenja 6. 6. 1906, umesto nastavka bitke sa životom, u već prepoznatljivom stilu je, pet minuta pre nego mu je došao kraj, 25. 5. u 5 sati pobedonosno „prozvao“ smrt rekavši: „Idem sada da umrem”, okrenuo leđa prisutnim svedocima događaja i otišao u večnost. Toga dana je u novinama osvanuo naslov da je „Na Dan mladosti u Novom Sadu umro najstariji sugrađan“. Prvi je bio i među kremiranim Novosađanima, a urna sa pepelom njegovih zemnih ostataka nalazi se smeštena u prvom odeljku Kolumbarijuma novosadskog Gradskog groblja.

Bio je i ostao u sećanjima mnogih sugrađana, pacijenata a posebno đaka, poštovalaca i sledbenika, snažan svetionik pokoljenjima: savestan i odgovoran lekar, human i čestit čovek, odmeren i mudar sagovornik, uporan i studiozan naučnik, dosledan i dovitljiv prijatelj, uspešan pedagog i talentovan predavač, elokventan i obrazovan, ozbiljan i pravičan, elegantan i gospodstven, čarobnjak reči i tumač večnih tajni ljudske duše, mađioničar dosetki, virtuoz govora i mudrac pronalaženja jednostavnih rešenja i u najtežim okolnostima.

Sećanja su spomenik tvrđi od kamena a nezaborav najbolji način da se potomci oduže precima – sećanje na njega spomenik je i svim lekarima zaslužnim za slavu legende doktora NEMANJE VURDELJE! Bio je umetnik struke i ponosimo se kao nastavljači njegovog rada i dela, velikog lekara, predavača, naučnika i narodnog prosvetitelja, korifeja i legende srpske, vojvođanske i jugoslovenske neurologije i psihijatrije. Poštovaoci profesorovog lika i dela, njegovi đaci i sledbenici, sa izrazima najveće zahvalnosti za sve što je učinio za naše struke, sećaćemo ga se sa zasluženim pijetetom i uverenjem da nema boljeg načina da mu se odužimo od nezaborava i čuvanja svih uspomena na njega i njegovo veliko delo.

Prof. dr Milorad Žikić

REGISTAR ZA 2023. GODINU

INDEKS AUTORA

INDEX KEY WORDS

INDEKS KLJUČNIH REČI

UPUTSTVO ZA AUTORE

Časopis ***Medicinski pregled*** objavljuje radove koji prethodno nisu objavljeni niti poslati u drugi časopis. U Časopisu mogu biti objavljeni radovi iz različitih oblasti biomedicine, koji su namenjeni lekarima različitih specijalnosti.

Od 1. januara 2013. godine *Medicinski pregled* je počeo da koristi usluge *e-Ur* − Elektronskog uređivanja časopisa. Svi korisnici sistema − autori, recenzenti i urednici, moraju biti registrovani korisnici sa jednom elektronskom adresom.

Korisnici časopisa treba da se registruju na adresi:
http://aseestant.ceon.rs/index.php/medpreg/user/register
Prijava rada treba da se učini na adresi:
http://aseestant.ceon.rs/index.php/medpreg/

U postupku prijave neophodno je da se pošalje saglasnost i izjava autora i svih koautora da rad nije delimično ili u celini objavljen ili prihvaćen za štampu u drugom časopisu. **Uz svaki rad, uz ostale meta podatke, mora biti naznačen i ORCID broj svakog autora.**

Elektronsko uređivanje časopisa obezbeđuje korišćenje sistema *CrossCheck*, koji prijavljene radove automatski proverava na plagijarizam i autoplagijarizam. Autori ne bi smeli da pošalju isti rad u više časopisa istovremeno. Ukoliko se to desi, glavni urednik časopisa *Medicinski pregled* ima pravo da rad vrati autorima bez prethodnog slanja rada na recenziju; da odbije štampanje rada; da se obrati urednicima drugih časopisa u koje je rad poslat ili da se obrati direktoru ustanove u kojoj su autori rada zaposleni.

Primaju se samo radovi koji su napisani na engleskom jeziku, uz sažetak rada i naslov rada koji treba da budu napisani na engleskom i srpskom jeziku.

Radove koji su pristigli u časopis *Medicinski pregled* pregleda jedan ili više članova Uređivačkog odbora Časopisa. Oni radovi koji su napisani prema pravilima Časopisa šalju se na anonimnu recenziju kod najmanje dva recenzenta, stručnjaka iz odgovarajuće oblasti biomedicine. Načinjene recenzije radova pregleda glavni urednik ili članovi Uređivačkog odbora i one nisu garancija da će rad biti prihvaćen za štampu. Materijal koji je pristigao u časopis ostaje poverljiv dok se rad nalazi na recenziji, a identitet autora i recenzenata su zaštićeni, osim u slučaju ako oni odluče drugačije.

U časopisu *Medicinski pregled* objavljuju se: uvodnici, originalni članci, prethodna ili kratka saopštenja, pregledni članci, stručni članci, prikazi slučajeva, članci iz istorije medicine i drugi članci.

1. Uvodnici – do 5 strana. Sadrže mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.

2. Originalni članci – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

3. Pregledni članci – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

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.

5. Stručni članci – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

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).*

Priprema rukopisa

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

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

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.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

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

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

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.

3. Tekst članka

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

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

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

Materijal i metode

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.

Rezultati

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.

Diskusija

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.

Zaključak

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.

4. Literatura

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.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG*, *GIF*, *TIFF*, *EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike.

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.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

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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.

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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.

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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.

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