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IMPORTANCE OF RISK FACTORS IN THE EFFECTIVENESS OF MEDICATION THERAPY IN PATIENTS WITH FUNCTIONAL LOWER EXTREMITY ISCHEMIA

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Analysis of the influence of risk factors on drug therapy measured by prolongation of the claudication distance in patients with functional lower extremity ischemia (FLEI) can significantly improve the individual approach to the treatment of these patients.

The aim of the study was to determine the impact of risk factors on the effectiveness of medicament therapy in patients with FLEI.

The study included 82 patients with diagnosed FLEI (Fontaine IIa, IIb), treated at the Clinic for Vascular Surgery of the University Clinical Center in Niš, starting from January 2020 to December 31, 2020.

After 6 months of examination, there was a statistically significant difference in the prolongation of claudication distance in relation to the therapeutic modality in woman (p = 0.03), patients with dyslipidemia (p = 0.001) and patients with hypertension (p = 0.02), noting that higher efficacy was achieved in the group of respondents who used cilostazol and acetylsalicylic acid (ASA).

Risk factors that have a significant effect on the applied therapeutic modality are female gender, dyslipidemia and hypertension, while age, obesity and male gender are risk factors where such correlation is not present. Cilostazol and ASA therapy were more effective than pentoxifylline and ASA therapy in the group of respondents suffering from hypertension and dyslipidemia as well as in women.

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***Key words**: risk factors, medication therapy, peripheral arterial disease*

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Introduction

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis with an increase in the prevalence of aging population, caused by a number of predisposing factors. Risk factors for coronary, renovascular, cerebrovascular and peripheral arterial disease are identical. Chronic progression, development and complications of atherosclerotic lesions or plaques are accelerated by risk factors such as gender, age, hereditary factors, smoking, hypertension, hyperlipidemia, chronic renal failure, obesity, diabetes, physical inactivity, inadequate diet and emotional stress (1).

Medicament therapy that is approved and has shown efficient in relieving the symptoms and prolongation of claudication distance involves the use of phosphodiesterase inhibitors, pentoxifylline and cilostazol (2, 3). In addition, the use of antithrombotic medicaments is a significant component in the treatment of PAD. The use of acetylsalicylic acid (ASA) and clopidogrel slows progression, reduces the percentage of graft occlusion after revascularization and reduces the risk of cardiovascular death by 25% in patients with PAD (4).

Peripheral vasodilators represent a potentially useful group of medicaments in the treatment of PAD (4). Pentoxifylline is a theophylline derivative with significant hemorrhoidal properties.

It can reduce the symptoms of claudication by decreasing blood viscosity and increasing the deformability of erythrocytes and leukocytes (5). However, the available guidelines for the treatment of PAD favor the use of cilostazol recommending IA in the treatment of symptomatic claudication (6).

Regarding the complexity of the occurrence, the impact of various risk factors and the progression of peripheral arterial disease, this prospective study aims to determine the relationship between the impacts of risk factors on the effectiveness of medicament therapy in patients with functional lower extremity ischemia (FLEI).

Patients and research methods

Patient group examined

The prospective clinical trial included patients with FLEI who were treated on an outpatient basis at the Clinic of Vascular Surgery of the Clinical Center in Niš in the period from January 2020 to December 2020.

The study included subjects who were first diagnosed with FLEI. The diagnosis was made according to anamnesis, clinical examination, dopplerechosonography and/or MSCT angiography of the main arteries of the lower extremities.

The criteria applied for inclusion in the study involved: patients with stage IIa and IIb disease according to Fontaine, in whom PAD of the lower extremities had been verified using Doppler sonography or MSCT angiography (7).

The criteria applied for exclusion from the study involved patients with I, III and IV stage PAD according to Fontaine, amputation of the lower extremities, ejection fraction ≤ 40%, chronic peritoneal dialysis and hemodialysis, malignancies and associated diseases leading to impaired general condition and physical fitness.

Methodology

The research protocol was approved by the Ethics Committee of the Faculty of Medicine in Niš (12-15637-2/5 dated December 24, 2019). The research completely comes to terms with the Helsinki Declaration on Ethical Treatment and it was conducted according to the principles of Good Clinical Practice (GCP). All patients were informed of the purpose of the study and they voluntarily signed a consent form. The research was designed in the form of a prospective cross-sectional study using a survey.

The investigation included a questionnaire with closed answers and different variants from dichotomous to combined, with open additional questions.

The classification of the respondents' disease stage was performed according to Fontaine: Stage I (asymptomatic); Stage IIa (moderate claudication distance (CD) > 200 m); Stage IIb (moderate to severe CD < 200 m); Stage III (ischemic pain at rest, CD up to 50 m) and stage IV (presence of ulceration and gangrene).

Claudication distance

In order to obtain reproducible results, the patients were given guidelines on how to measure claudication distance. The respondents were recommended to walk at a constant frequency and speed for a certain distance in order to obtain an objective assessment of step frequency (number of steps) and walking speed. The values of claudication distance were determined on the basis of the distance the respondents had traveled, expressed by the number of steps using the following model:

If a person walks at a constant speed **v** and frequency **f** for a given distance **s** with the number of steps **n** in the time period **t**, then the walking frequency can be calculated according to the following formula (8, 9):

Walking frequency: $f = \frac{n}{t}$

Walking speed: $v = \frac{s}{t}$

Step length: $sl = \frac{s}{n}$

Taking into account that step length differs between men and women, it is necessary to introduce the following correction factor in accordance with the height of respondents:

Step length in men (cm) = sl_m = 0.415 x height (cm)

Step length in women (cm) = sl_w = 0.413 xheight (cm)

The above formulas show that the length of the traveled distance can be calculated in the following way:

Traveled distance $= s = sl \; x \; n$

Traveled distance in men (m) = sl_m x n $= \frac{0.415 \; x \; height \; (cm) \; x \; number \; of \; steps}{100}$

Traveled distance in women (m) = sl_w x n = $\frac{0.413 \; x \; height \; (cm) \; x \; number \; of \; steps}{100}$

The claudication distance (CD) of the patients (expressed in meters) was determined and compared at the first examination, and control examinations after three and six months starting from the introduction of medicament therapy.

The differences in the obtained values of claudication distance in the indicated periods determined the prolongation of claudication distance (PCD) values.

Respondent groups

In order to perform an adequate data analysis based on demographic characteristics, therapeutic modalities, risk factors and physical activity, the following respondent groups were formed:

- gender: male and female respondents;
- age: < 65 years and ≥ 65 years;
- medicament therapy:
- the first group included the patients administered pentoxifylline 400 mg three times a day and acetyl-salicylic acid 100 mg once a day (pentoxifylline and ASA);
- the second group included the patients administered cilostazol 100 mg twice a day and acetyl-salicylic acid 100 mg once a day (cilostazol and ASA);
- presence/absence of risk factors: smoking, obesity, diabetes, dyslipidemia and hypertension,

Determination of body mass index (BMI) was performed by a calculation based on the following formula: BMI = body weight (BW)/body height $(BH)^2$. The patients were considered obese if their BMI was over 30 kg/m^2.

The presence of diabetes, dyslipidemia and hypertension was established by adequate specialist and subspecialist branches of medicine.

Statistical data processing

The statistical analysis was performed with the software package SPSS 16.0 for Windows. The methods included descriptive and analytical statistics. Continuous variables were described as mean (X) and standard deviation (SD), while proportional percentages were used for category variables. The normality of distribution was assessed by the Kolmogorov-Smirnov test, while the homogeneity of distribution was tested by the Levin test. The significance of the difference for continuous variables, with normal distribution, was estimated by parametric methods. The t-test for independent samples was used to compare two groups of respondents, and one-way ANOVA was used for three or more groups, while the Chi-square test was used for nonparametric variables. The difference was marked significant if $p < 0.05$. In the case of a statistically significant difference, the Tukey HSD test was used. Spearman's correlation was used to estimate the correlation.

Results

The study included 82 patients diagnosed with FLEI treated at the Clinic for Vascular Surgery of the Clinical Center in Niš, starting from January 2020 to December 31st, 2020. In the conducted research, 48.78% of the subjects used pentoxifylline and ASA, while 51.22% of the respondents were treated with cilostazol and ASA.

The basic demographic characteristics of patients and risk factors are shown in Tables 1 and 2.

Of the total number of the examined patients, 49 (59.76%) were male and 33 (40.24%) were female. The average age of the respondents was 67.62 years (SD = 8.22). The youngest respondent was 48, and the oldest was 82 years old.

In the largest number of patients with FLEI, smoking was the most common risk factor (76.82%), followed by hypertension (75.60%), while dyslipidemia was the least common (63.71%).

The values of CD in relation to the choice and duration of medicament therapy are shown in Table 3.

One-factor analysis of covariance compared the effectiveness of applied therapeutic modalities on CD values between the first and control examinations after 3 and 6 months. The independent variable was the type of therapy (cilostazol and ASA and pentoxifylline and ASA), and the dependent variables were CD values after 3 and 6 months. The results of CD at the first examination were used as a covariate in the analysis, Preliminary checks established that the assumptions about normality, linearity of variance homogeneity, regression slope homogeneity and covariate measurement reliability were not violated.

The results of the analyzed therapeutic modalities showed that there was no statistically significant difference in the values of CD three months after the therapy had been introduced ($F(1.79) = 0.82$; $p = 0.37$; partial eta square = 0.1). CD analysis 6 months after the therapy had been introduced showed a statistically significant difference between the analyzed medicament therapy ($F(1, 79) = 5.06$; $p = 0.027$; partial eta square = 0.6), whereas the prolongation of claudication distance was greater in the group of patients who received cilostazol and ASA.

In order to examine the relationship between risk factors and the effectiveness of medicament therapy in patients with FLEI, the correlation of PCD patients with the following risk factors was analyzed: gender, age, obesity, diabetes, dyslipidemia, hypertension and the number of risk factors.

Table 1. Demographic characteristics of patients

Gender	N	%
Male	49	59.76
Female	33	40.24
Age		
< 65	29	35.37
≥ 65	53	64.63
Total	82	100

Table 2. Risk factors of patients

Factor	N	%
Obesity	59	71.95
Diabetes	57	69.51
Dyslipidemia	52	63.71
Hypertension	62	75.60

Table 3. Values of CD in relation to the choice and duration of medicament therapy (m)

	Cilostazol + ASA			Pentoxifylline + ASK		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
First examination	42	203.10	57.66	40	200.25	71.09
After 3 months	42	265.24	113.05	40	249.00	113.35
After 6 months	42	367.98*	168.28	40	310.13*	162.82

Table 4. Influence of risk factors and applied therapy on PCD (m)

Gender	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
Male						
After 3 months	23	60.43	76.91	26	56.92	67.26
After 6 months	23	133.48	145.51	26	171.73	127.40
Female						
After 3 months	17	32.94	38.20	16	70.63	76.33
After 6 months	17	77.94*	69.60	16	153.75*	120.31
Age	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
< 65 years						
After 3 months	15	71.33	88.77	14	101.07	89.85
After 6 months	15	142.00	171.44	14	247.86	154.88
≥ 65 years						
After 3 months	25	35.20	39.96	28	42.68	49.28
After 6 months	25	90.60	75.61	28	123.39	79.28
Obesity	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD

< 30 kg/m²						
After 3 months	12	93.33	79.61	11	134.09	87.52
After 6 months	12	197.08	147.01	11	292.27	154.68
≥ 30 kg/m²						
After 3 months	28	29.64	45.99	31	36.61	40.26
After 6 months	28	72.50	87.22	31	119.68	69.52
Diabetes	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
Without diabetes						
After 3 months	12	47.08	62.61	13	85.00	86.29
After 6 months	12	146.67	122.54	13	210.77	144.08
With diabetes						
After 3 months	28	49.46	66.03	29	51.90	60.70
After 6 months	28	94.11	119.43	29	144.31	109.77
Dyslipidemia	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
Without dyslipidemia						
After 3 months	17	79.12	82.12	13	116.15	92.65
After 6 months	17	170.88	159.77	13	257.69	167.33
With dyslipidemia						
After 3 months	23	26.30	34.19	29	37.93	39.83
After 6 months	23	64.78**	50.01	29	123.28**	67.60
Hypertension	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
Without hypertension						
After 3 months	11	57.27	82.23	9	108.89	106.32
After 6 months	11	174.09	144.77	9	241.67	195.46
With hypertension						
After 3 months	29	45.52	57.37	33	49.39	52.11
After 6 months	29	85.52*	103.74	33	143.94*	88.91

Discussion

At the first examination, the values of claudication distance between the groups of patients who received pentoxifylline and ASA and cilostazol and ASA were not significantly different in terms of statistics. Also, the results show that there was no statistically significant difference in the values of CD three months after the introduction of therapy between the analyzed therapeutic modalities. CD analysis 6 months after the introduction of therapy revealed a statistically significant difference ($p < 0.05$) between the treatment modalities, noting that the prolongation of claudication distance was greater in the group of patients who received cilostazol and ASA compared to the group of patients who received pentoxifylline and ASA.

The first clinical study to compare the efficacy of pentoxifylline and cilostazol in the treatment of intermittent claudication was conducted by Dawson et al. The study included 698 patients with intermittent claudication, and the efficacy and safety were monitored for 24 weeks. At the end of the observed period, the group of patients who used cilostazol, achieved significantly better PCD results, compared to the group of patients who used pentoxifylline (94 m vs. 74 m) (10). Singh et al. came to similar observations in their research conducted in India. Namely, the therapeutic effects of pentoxifylline and cilostazol were monitored in 79 patients with PAD for 12 weeks with a pronounced superior effect on PCD in the group of respondents who used cilostazol (11). The higher efficacy of cilostazol in relation to pentoxifylline was also noticed in research conducted by Gupta et al. (12). The study conducted in the United Kingdom also highlighted the advantage of cilostazol over pentoxifylline in the treatment of PAD from a

pharmacoeconomic aspect (13). The obtained results of the conducted research match the results of the previously mentioned studies. The unique combination of antiplatelet, vasodilatory and antiproliferative effects of cilostazol makes it a preferable medicament for FILE therapy. Long-term use of cilostazol did not show significant differences in the frequency of bleeding or cardiovascular and cerebrovascular complications compared to the use of pentoxifylline (14). The results of the research conducted so far suggest that cilostazol will be an inevitable therapeutic option for reducing the symptoms and improving the quality of life in patients with intermittent claudication (15).

Recent research indicates that women suffer from this chronic disease almost as frequently as men, taking into account the phenomenon of the twentieth century (women live longer and make greater part of the elderly population) (16, 17). Accordingly, the main goals of treatment of peripheral arterial disease are similar for both genders and they relate to reducing morbidity/mortality, reducing the symptoms and improving the quality of life (18). The research results indicate that there was no statistically significant difference in terms of PCD at follow-up examinations after 3 and 6 months in relation to respondents' gender. The research results indicate that in women, at the follow-up examination after 6 months, there was a statistically significant difference ($p < 0.05$) in PCD between the applied therapeutic modalities, noting that higher efficacy was achieved in the group of respondents who used cilostazol and ASA in relation to the group of respondents who used pentoxifylline and ASA. There are very few available studies that have compared the efficacy of medicament therapy in relation to respondents' gender. In their study, Pande et al. confirmed that there was no statistically significant difference in the efficacy of medicament therapy in relation to respondents' gender, which matches the results of this study (19). However, in contrast to medicament therapy, the results of a study conducted by Gallagher et al. have shown that the endovascular approach in the treatment of individual lesions that lead to critical ischemia of lower extremities has more effective results in women, and the choice should be adjusted to respondents' gender (20).

In relation to the applied therapeutic modalities, there was no statistically significant difference in PCD at control examinations in the group of respondents under the age of 65 and the group of respondents over the age of 65. The results of the research are in accordance with previously conducted studies in which the efficacy of pentoxifylline and cilostazol was confirmed regardless of the respondents' age (2, 21).

The results of the study indicate that in relation to therapeutic modalities, there was no statistically significant difference in PCD at follow-up examinations in the group of respondents with BMI $< 30 kg/m^2$ and the group of respondents with BMI $\geq 30 kg/m^2$. Previous studies did not take into account the impact of obesity on the outcome of PAD therapy, as obesity was the exclusion criterion in most cases. However, the antiatherogenic and anti-inflammatory potential of cilostazol could favor the use of this medication in obese patients with intermittent claudication. This is supported by the results of research conducted by Kim et al. showing that an eight-week administration of cilostazol contributes to a significant increase in lipoprotein lipase and inhibition of cytokine production (22). Further research in the field of investigating the effect of cilostazol in obese patients with intermittent claudication will confirm these assumptions.

Diabetes is one of the most important risk factors leading to PAD. Literature data indicate that the prevalence of PAD in diabetics over the age of 50 is about 30%, while in patients with critical limb ischemia, diabetes is present in more than 50% of cases (23). In relation to therapeutic modalities, there was no statistically significant difference between PCD at follow-up examinations in the group of patients with diabetes and the group of patients without diabetes. The therapy outcome in patients with diabetes mellitus and PAD depends on the interaction between factors such as comorbidities, the presence of infection, neuropathy and the immune response (24). Poor glycemic control is associated with a higher prevalence of PAD and the risk of adverse outcomes, as well as reduced success of therapy, both medication and surgical modalities (25).

Dyslipidemia is a variable risk factor in the development of PAD. It is a disorder that occurs as a result of accelerated synthesis or slow breakdown of lipoproteins involved in the transport of cholesterol and triglycerides in plasma. It is generally accepted that hyperlipoproteinemia is one of the most important independent risk factors for atherosclerosis and peripheral vascular disease (26). The results of the conducted research show that the presence of dyslipidemia had a statistically significant effect on the efficacy of medicament therapy. A statistically significant difference ($p < 0.01$) was found in the group of respondents suffering from dyslipidemia at the control examination after 6 months, noting that higher efficacy was achieved in the group of respondents who used cilostazol and ASA compared to the group of respondents who used pentoxifylline and ASK. Cilostazol is a medicament that, in addition to vasodilators and antithrombotic medicaments, also has significant effects at the level of atherogenic dyslipidemia. It is a medication that can improve the pro-atherogenic lipid profile in patients with PAD or diabetes by lowering serum triglycerides while

increasing HDL levels. In addition, cilostazol exerts its effect by acting on pro-atherogenic lipoproteins and apolipoproteins (27).

Hypertension is a factor that increases the risk of PAD by 2–3 times. In the conducted research, 75.6% of patients had both PAD and hypertension (28). In the group of respondents with hypertension, the results of the research indicate that at the control examination after 6 months there was a higher efficacy of cilostazol and ASA compared to pentoxifylline and ASA ($p < 0.05$).

Conclusion

According to the study results, it can be concluded that cilostazol and ASA therapy is more effective in prolonging claudication distance compared to pentoxifylline and ASA therapy in patients with functional ischemia of the lower extremities.

Risk factors that have a significant effect on the applied therapeutic modality are female gender, dyslipidemia and hypertension, while age, obesity and male gender are risk factors where such correlation is not present. Cilostazol and ASA therapy was more effective than pentoxifylline and ASA therapy in the group of respondents suffering from hypertension and dyslipidemia as well as in women.

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UTICAJ FAKTORA RIZIKA NA EFIKASNOST MEDIKAMENTOZNE TERAPIJE KOD BOLESNIKA SA FUNKCIONALNOM ISHEMIJOM DONJIH EKSTREMITETA

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Analiza uticaja faktora rizika na medikamentoznu terapiju, merena produženjem klaudikacione distance, kod bolesnika sa funkcionalnom ishemijom donjih ekstremiteta (FIDE) može značajno unaprediti individualni pristup u lečenju.

Cilj rada bio je da se utvrdi uticaj faktora rizika na efikasnost medikamentozne terapije kod bolesnika sa FIDE.

Istraživanjem su obuhvaćena 82 bolesnika sa dijagnostikovanom FIDE (Fontaine IIa, IIb) lečena na Klinici za vaskularnu hirurgiju Univerzitetskog kliničkog centra u Nišu u periodu od januara do 31. decembra 2020. godine.

Nakon šest meseci pregleda, uočena je statistički značajna razlika u produženju klaudikacione distance u odnosu na terapijski modalitet kod žena (p = 0,03), bolesnika sa dislipidemijom (p = 0,001) i bolesnika sa hipertenzijom (p = 0,02), uz napomenu da je veća efikasnost postignuta u grupi ispitanika koji su koristili cilostazol i acetilsalicilnu kiselinu (ASK).

Faktori rizika koji umnogome utiču na primenjeni terapijski modalitet jesu pripadnost ženskom polu, dislipidemija i hipertenzija; uzrast, gojaznost i pripadnost muškom polu faktori su rizika kod kojih navedena korelacija nije prisutna. Terapija cilostazolom i ASK-om bila je efikasnija od terapije pentoksifilinom i ASK-om u grupi ispitanika sa hipertenzijom i dislipidemijom, kao i kod žena.

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***Ključne reči**: faktori rizika, medikamentozna terapija, periferna arterijska bolest*

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EFFICACY OF DRUG THERAPY IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE IN RELATION TO SMOKING

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Peripheral arterial disease is one of the manifestations of atherosclerosis that manifests itself primarily in the peripheral arteries of the lower extremities and the aorto-iliac segment. The largest number of patients, about 90%, have functional ischemia (Stage IIa and IIb according to Fontaine). For these patients, the therapy of choice is medication consisting of a combination of acetylsalicylic acid, cilostazol and pentoxifylline. Smoking is a very significant risk factor for the development of peripheral arterial disease and is also one of the most significant outcome modifiers. The study included 82 patients diagnosed with functional ischaemia of the lower extremities treated at the Clinic of Vascular Surgery of the Clinical Center in Niš, starting from January 2020 to December 31, 2020. Smoking was present in 76.82% of respondents. In the research conducted, 48.78% of respondents used pentoxifylline + acetylsalicylic acid, while 51.22% of respondents were treated with cilostazol + acetylsalicylic acid. Results showed the extension of the claudication distance after 6 months was significantly greater in the group of patients who used cilostazol + acetylsalicylic acid. In a subgroup of patients smoking > 20 cigars daily and with > 20 years of smoking there was a significant increase in claudication distance after 6 months in the cilostazol + acetylsalicylic acid group compared to pentoxifylline + acetylsalicylic acid group. In conclusion, the number of cigarettes/day and length of smoking experience have a significant effect on the applied therapeutic modality in patients with peripheral arterial disease. Cilostazol + acetylsalicylic acid therapy was more effective than pentoxifylline + acetylsalicylic acid.

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Key words: *peripheral arterial disease, medical treatment, smoking*

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Introduction

Peripheral arterial disease (PAD) is one of the manifestations of atherosclerosis that manifests itself primarily in the peripheral arteries of the lower extremities and the aorto-iliac segment and is a disorder in the normal functioning of the arterial system that leads to reduced blood flow in the extremities. The main clinical manifestation of functional ischemia of the lower extremities is intermittent claudication (1). Risk factors for PAD are hypertension, dyslipidemia, smoking, diabetes and genetic load (2). Considering that atherosclerosis is a systemic disease, 50%–75% of patients with peripheral arterial disease also suffer from coronary or cerebrovascular disease (3).

PAD therapy consists of risk factor control, drug therapy, endovascular and open surgical treatment.

The largest number of patients with PAD, about 90%, have functional ischemia (Stage IIa and IIb according to Fontaine). For these patients, the therapy of choice is medication consisting of a combination of ASA, cilostazol and pentoxifylline (4).

Pentoxifylline is a xanthine derivative whose main mechanism of action is haemolytic. Pentoxifylline enhances erythrocyte deformability, reduces blood viscosity and reduces platelet aggregation. Cilostazol is a phosphodiesterase III inhibitor and its main mechanisms of action in the treatment of PAD are relaxation of smooth muscle cells in blood vessels, stimulation of angiogenesis and antiaggregation. Numerous studies have shown the superiority of cilostazol over pentoxifylline, so it has largely supplanted pentoxifylline as the drug of first choice (5). However, cilostazol has numerous side effects such as dizziness, palpitations and nausea, which

leads to very poor long-term adherence to therapy. It has been shown that within 36 months, more than 60% of patients discontinue cilostazol therapy, leaving room for further use of pentoxifylline regardless of the superior effect of cilostazol (6).

Smoking is a very significant risk factor for the development of PAD and compared to non-smokers, active smokers have a five times higher risk of developing PAD. The effect of smoking on the cardiovascular system is very harmful considering that it damages the endothelium of the arteries and has an atherogenic effect. The mechanism by which smoking affects the development and progression of PAD is via the carbon monoxide and increased carboxy-hemoglobin levels (7). Also, smoking leads to a reduction in blood flow by activating vasospastic mechanisms and increasing blood viscosity. These disorders lead to the consequent activation of coagulation factors and a decrease in the elasticity of erythrocytes. Literature data have shown that there is a positive association between cigarette use and increased levels of triglycerides, cholesterol and low-density lipoprotein (LDL) with a decrease in the level of protective high-density lipoprotein (HDL) (8). A meta-analysis by Willigendael et al., which included 29 studies, showed that smoking in patients who underwent a revascularization procedure caused up to 3 times more frequent graft thrombosis compared to non-smokers. In this relationship between smoking and graft occlusion, the number of cigarettes consumed and the length of smoking experience had a significant relationship, while the type of prosthetic material was not significant. Cessation of smoking after performing the revascularization procedure allowed the patency of the grafts to be equivalent to that of non-smokers (9). Research that evaluates the effect of smoking on medical or conservative PAD therapy is practically non-existent.

This prospective study aims to determine the influence of smoking on the effectiveness of drug therapy in patients with functional ischemia of the lower extremities (FILE).

Patients and research methods

The examined group of patients

The prospective clinical trial included patients with FILE who were treated on an outpatient basis at the Clinic of Vascular Surgery of the Clinical Center in Niš in the period from January 2020 to December 2020.

Respondents who were diagnosed with FILE for the first time were included in the research. The diagnosis was made on the basis of history, clinical examination, Doppler echosonography and/or MDCT angiography of the main arteries of the lower extremities.

The criteria for inclusion in the study encompassed patients with stage IIa and IIb disease according to Fontaine, who had PAD of the lower extremities verified by Doppler sonography or MDCT angiography (10). The criteria for exclusion from the study encompassed patients with: I, III and IV stage of PAD according to Fontaine, amputation of the lower extremities, ejection fraction ≤ 40%, chronic peritoneal dialysis and hemodialysis, malignancies and associated diseases that lead to impaired general condition and physical condition.

Methodology

The research protocol was approved by the Ethics Committee of the Faculty of Medicine in Niš (12-15637-2/5 dated 12/24/2019). The research was fully adapted to the Declaration of Helsinki on ethical behavior and conducted according to the principles of Good Clinical Practice (GCP).

The classification of the disease stage was performed according to Fontaine: I stage (asymptomatic); IIa stage (moderate CD > 200 m); IIb stage (moderate to severe CD < 200 m); III stage (ischemic pain at rest, CD up to 50 m) and IV stage (presence of ulceration and gangrene). Patients with Fontaine stage IIa and IIb disease were included in the study.

Claudication distance

In order to obtain reproducible results, patients were given guidelines on how to measure the claudication distance. Subjects were advised to walk at a constant frequency and speed for a certain distance to obtain an objective assessment of step frequency (number of steps) and walking speed. The values of the claudication distance were determined based on the distance covered by the subject, expressed by the number of steps using the following model:

If a person walks at a constant speed v and frequency f for a given distance s with the number of steps n in a time period t, then the walking frequency can be calculated by the following formula (11):

$$Frequency: f = n/t$$
$$Walking\ speed: v = s/t$$
$$Step\ length: sl = s/n$$

Bearing in mind that the length of steps in men and women is different, it is necessary to introduce the following correction factor in the scale with the height of the examinee:

-Men step length (MSL) = 0.415 x height in cm

-Women step length (WSL) = 0.413 x height in cm

From the mentioned formulas, it follows that the length of the traveled path can be calculated as follows:

-Claudication distance (CD) = MSL or WSL x n

The claudication distance of the patients (expressed in meters) was determined and compared at the first examination and control examinations after three and six months after the introduction of drug therapy, whereby the values of the change/extension of the claudication distance (CCD) were obtained.

Groups of participants

Groups were formed based on the applied therapeutic modalities and the presence/absence of smoking habits in a ratio of 1 to 1.

Based on the applied drug therapy, the first group consisted of patients who received pentoxifylline 400 mg three times a day and acetylsalicylic acid (ASA) 100 mg once a day (pentoxifylline + ASA) and the second group consisted of patients who received cilostazol 100 mg twice a day and acetylsalicylic acid 100 mg once a day (cilostazol + ASA).

Statistical data processing

Statistical analysis was performed using the SPSS 16.0 software package for Windows. Methods of descriptive and analytical statistics were used. Continuous variables were described as average value ($\bar{X}$) and standard deviation (SD), while proportions (percentages) were used for categorical variables. The normality of the distribution was assessed by the Kolmogorov-Smirnov test, while the homogeneity of the distribution was tested by the Levin test. The assessment of the significance of the difference for continuous variables, with a normal distribution, was performed using parametric methods. The t-test for independent samples was used to compare two groups of respondents, and one-way ANOVA was used for three or more groups, while the Chi-square test was used for non-parametric variables. The difference is marked as significant if $p < 0.05$. In the case of a statistically significant difference, Tukey's HSD test was used. Spearman's correlation was used to assess the correlation.

Results

The study included 82 patients diagnosed with FILE treated at the Clinic of Vascular Surgery of the Clinical Center in Niš, starting from January 2020 to December 31, 2020. Smoking was present in 76.82% of respondents. In the research conducted, 48.78% of respondents used pentoxifylline + ASA, while 51.22% of respondents were treated with cilostazol + ASA

CD (claudication distance) values in relation to the choice and duration of drug therapy are shown in Table 1.

The results of the analyzed therapeutic modalities showed that there was no statistically significant difference in CD values after three months from the therapy introduction ($F(1.79) = 0.82$; $p = 0.37$; partial eta square = 0.1). Analysis of CD 6 months after the introduction of therapy found a statistically significant difference between the analyzed drug therapies ($F(1.79) = 5.06$; $p = 0.027$; partial eta squared = 0.6), the extension of the claudication distance was significantly greater in the group of patients who used cilostazol + ASA.

The influence of smoking and applied therapy on CCD is shown in Table 2.

In the group of subjects who did not smoke, there was no statistically significant CCD in relation to the applied therapy ($t(17) = 0.19$, $p = 0.85$; MD = -7.95; 95% CI: -94.76 to 78 .85; $\eta 2 < 0.01$) at the follow-up examination after 3 months. Static significance was not found even after 6 months of therapy initiation ($t(17) = 0.02$, $p = 0.98$; MD = -71.25; 95% CI: -346.46 to 203.96; $\eta 2 < 0.01$). At the follow-up examination after 3 months in smokers, there was no statistically significant CCD in relation to the applied therapy ($t(61) = 0.85$, $p = 0.40$; MD = -12.83; 95% CI: -43.05 to 17.38; $\eta 2 = 0.01$). Also, static significance was not found even after 6 months of therapy initiation ($t(61) = 2.48$, $p = 0.016$; MD = -63.28; 95% CI: -114.33 to -12.23; $\eta 2 = 0.09$).

The influence of the number of cigarettes/day and the applied therapy on CCD is shown in Table 3.

Table 1. CD values in relation to the choice and duration of drug therapy (m)

	Cilostazol + ASA			Pentoxifylline + ASK		
	N	$\bar{X}$	SD	N	$\bar{X}$	SD
First review	42	203.10	57.66	40	200.25	71.09
After 3 months	42	265.24	113.05	40	249.00	113.35
After 6 months	42	367.98 *	168.28	40	310.13*	162.82

*$p < 0.05$

Table 2. Influence of smoking and applied therapy on prolongation of claudication distance (m)

	ASA + pentoxifylline			ASA + cilostazol		
	N	$\bar{X}$	SD	N	$\bar{X}$	SD
Non-smokers						
After 3 months	8	72.50	91.77	11	80.45	86.21
After 6 months	8	222.50	130.69	11	220.91	167.45
Smokers						
After 3 months	32	42.81	55.73	31	55.65	64.04
After 6 months	32	81.72	102.72	31	145.00	99.82

Table 3. Influence of the number of cigarettes/day and applied therapy on the extension of the claudication distance (m)

	ASA + pentoxifylline			ASA + cilostazol		
	N	$\bar{X}$	SD	N	$\bar{X}$	SD
Smoking ≤ 20 cigarettes						
After 3 months	12	47.92	60.84	11	57.27	58.07
After 6 months	12	95.42	140.01	11	123.18	74.27
Smoking > 20 cigarettes						
After 3 months	20	39.75	53.84	20	54,75	68.55
After 6 months	20	73.50*	75.34	20	157.00*	111.37

*$p < 0.01$

In the group of subjects smoking ≤ 20 cigarettes/day, there was no statistically significant CCD in relation to the applied therapy ($t(21) = 0.38$, $p = 0.71$; MD = -9.36; 95% CI: -61 .04 to 42.33; $\eta 2 = 0.01$) at the follow-up examination after 3 months. Static significance was not found even after 6 months of initiation of therapy ($t(21) = 0.59$, $p = 0.56$; MD = -27.77, 95% CI: -126.34 to 70.81; $\eta 2 = 0.02$).

At the follow-up examination after 3 months in the group of subjects who smoked > 20 cigarettes/day, there was no statistically significant CCD in relation to the applied therapy ($t(38) = 0.77$, $p = 0.45$; MD = -15.00; 95% CI: -54.46 to 24.46; $\eta 2 = 0.02$). However, at the follow-up examination after 6 months, statistical significance was observed in terms of CCD between the analyzed groups ($t(38) = 2.78$, $p = 0.008$; MD = -83.50; 95% CI: -144.37 to -22 .63; $\eta 2 = 0.17$), significantly higher efficiency was achieved in the group of subjects who applied cilostazol + ASA.

The influence of length of smoking experience and applied therapy on CCD is shown in Table 4.

Table 4. Influence of the length of smoking experience and applied therapy on the extension of the claudication distance (m)

	ASA + pentoxifylline			ASA + cilostazol		
	N	$\bar{X}$	SD	N	$\bar{X}$	SD
Smoking duration ≤ 20 years						
After 3 months	8	63.13	93.46	5	77.00	79.73
After 6 months	8	137.50	174.03	5	164.00	91.41
Smoking duration > 20 years						
After 3 months	2	36.04	36.56	26	51.54	61.61
After 6 months	2	63.13*	59.67	26	141.35*	102.64

In the group of subjects with smoking experience ≤ 20 years, there was no statistically significant CCD in relation to the applied therapy ($t(11) = 0.27$, $p = 0.79$; MD = -13.88; 95% CI: -125 .19 to 97.44; $\eta 2 = 0.01$) at the follow-up examination after 3 months. Static significance was not found even after 6 months of therapy initiation ($t(11) = 0.31$, $p = 0.76$; MD = -26.50; 95% CI: -213.92 to 160.92; $\eta 2 = 0.01$).

At the follow-up examination after 3 months, in the group of subjects who smoked > 20 years, there was no statistically significant CCD in relation to the applied therapy ($t(48) = 1.07$, $p = 0.29$; MD = -15.50; 95% CI: -44.62 to 13.62; $\eta 2 = 0.02$). However, at the follow-up examination after 6 months, statistical significance was observed in terms of CCD between the analyzed groups ($t(48) = 1.07$, $p = 0.002$; MD = -78.22; 95% CI: -126.49 to -29 .95; $\eta 2 = 0.18$), significantly higher efficiency achieved in the group of subjects who applied cilostazol + ASA.

Discussion

The role of smoking in the etiopathogenesis of PAD has been known for more than a hundred years. Although the effects of smoking as a risk factor have been studied mostly in coronary artery disease (CAD), studies have shown a greater significance in the development of PAD compared to CAD. Smoking, together with diabetes, is the most significant risk factor for PAD, with a 4 times higher incidence compared to the non-smoking population (12). The study by He et al. showed the association of PAD with smoking, with a ratio of 1.5:1 in favor of smokers. Also, this research showed that quitting smoking for more than 10 years significantly reduced the risk of PAD, practically eliminating it (13). Tobacco smoke contains thousands of substances that can have toxic effects on health. The substances that attract the most attention of researchers are nicotine and carbon monoxide. The pathophysiological mechanisms by which nicotine and carbon monoxide lead to the development of atherosclerosis and PAD are numerous (14).

These substances lead to: endothelial dysfunction, increased adhesion of leukocytes and aggregation of platelets to the endothelium, increased triglycerides and LDL, insulin resistance, increased activity of fibrinogen, increased expression of tissue factor, vasoconstriction and increased oxidative stress. In addition, these toxic substances increase the adhesion of monocytes to endothelial cells, which is one of the first steps in the development of atherosclerosis (15).

The results of the research show that in relation to the therapeutic modalities, there was no statistically significant difference in CCD at the follow-up examinations in the group of non-smokers and smokers. However, the research shows that at the follow-up examination after 6 months, the number of cigarettes/day and the length of smoking experience had a statistically significant effect on CCD in relation to the applied therapeutic modalities, noting that cilostazol + ASA was more effective than pentoxifylline + ASA in the group of subjects who smoke > 20 cigarettes/day ($p < 0.01$) and who smoke for > 20 years ($p < 0.01$).

These results can largely be explained by the proven effects of cilostazol on improving the endothelium-dependent vasodilator response in smokers (16). A randomized prospective study on patients implanted with a drug-eluting stent

showed that cilostazol eliminated the negative impact of smoking on adverse outcomes after stent implantation. One of the main conclusions of the study was that smokers who were treated with cilostazol and dual antiplatelet therapy had a similar outcome to non-smokers, while in the group of patients treated only with dual antiplatelet therapy, the outcome was significantly better in non-smokers. That is to say, that smoking stimulates the antiplatelet effects of cilostazol. The main pharmacologically active metabolites of cilostazol are formed in the body through cytochrome P450 (CYP3A4 and CYP 2C19). Bearing in mind that there is very little data on the influence of smoking on the pharmacokinetics of cilostazol, it can be assumed that nicotine can lead to inhibition of metabolism and an increase in the concentration of active metabolites of cilostazol in plasma (17). Cilostazol increases the endothelium-dependent vasodilatation of the brachial artery after artificial ischemia by up to 50% in smokers (18). Similar effects were shown for the femoral artery (19). An experiment on rats was conducted where the rats were divided into three groups: treated with cilostazol, aspirin and a control group. Rats were exposed to nicotine smoke for one minute and one hour after, the pial blood vessels were observed. It was confirmed that there was nicotine-induced constriction of blood vessels in the group treated with aspirin and in the control group, while vasoconstriction was absent in the group treated with cilostazol (20).

Smoking and PAD are closely related. A meta-analysis of 17 studies showed a 2.2-fold higher prevalence of symptomatic PAD in smokers compared to nonsmokers (21). Smoking accelerates the progression of PAD and leads to the progression of stable claudication to symptoms of critical lower limb ischemia (22). Yataco and Gardner investigated the acute effects of smoking on the reduction of the AB index in chronic smokers with PAD. The research included 10 chronic smokers who had smoking and non-smoking days. The non-smoking day meant that the patients refrained from smoking and caffeinated drinks 12 hours before the test, and the smoking day meant smoking two filter cigarettes 10 minutes before the test. After the analysis of the obtained ABI values, significantly higher values were proven, during the non-smoking day (23). The influence of smoking on the occurrence of PAD is proportional to the number of cigarettes consumed, so those who smoke 30 or more cigarettes per day have a significantly higher incidence of PAD than those who smoke up to 10 cigarettes, regardless of gender and age. Also, the length of smoking experience was significantly associated with the risk of developing PAD (24). Research by Lassil et al. showed a direct correlation between the number of cigarettes consumed and the frequency of amputations in patients with PAD. The frequency of amputations has been proven to be 21% in heavy smokers, compared to about 2% in moderate smokers (25).

On the other hand, it is necessary to look at the protective effects that cilostazol can achieve at the level of the cardiovascular system in the case of the presence of the nicotine effect (26). Therefore, its application in smokers with PAD may be justified in order to inhibit adverse events caused by cigarette consumption.

Conclusion

The number of cigarettes/day and length of smoking experience have a significant effect on the applied therapeutic modality in patients with PAD. Cilostazol + ASA therapy was more effective than pentoxifylline + ASA therapy in the group of smokers who had smoked > 20 cigarettes/day for > 20 years.

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EFIKASNOSTI MEDIKAMENTOZNE TERAPIJE BOLESNIKA SA PERIFERNOM ARTERIJSKOM BOLEŠĆU U ZAVISNOSTI OD PUŠAČKIH NAVIKA

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Periferna arterijska bolest (engl. *peripheral arterial disease* – PAD) jeste jedna od manifestacija ateroskleroze, koja se manifestuje prvenstveno u perifernim arterijama donjih ekstremiteta i aorto-ilijakalnog segmenta. Najveći broj bolesnika, oko 90% njih, ima funkcionalnu ishemiju (Stadijum IIa i IIb prema Fontaineu). Terapija izbora za ove bolesnike sastoji se od kombinacije acetilsalicilne kiseline, cilostazola i pentoksifilina. Pušenje je veoma značajan faktor rizika za razvoj PAD-a i, takođe, jedan od najznačajnijih modifikatora ishoda lečenja. Studijom su obuhvaćena 82 bolesnika sa dijagnozom ishemije donjih ekstremiteta (FIDE) lečena na Klinici za vaskularnu hirurgiju Kliničkog centra u Nišu u periodu od januara do 31. decembra 2020. godine. Pušači su činili 76,82% ispitanika. U sprovedenom istraživanju, 48,78% ispitanika koristilo je pentoksifilin + acetilsalicilnu kiselinu, dok su 51,22% ispitanika lečena cilostazolom + acetilsacilnom kiselinom. Rezultati su pokazali da je produženje klaudikacione distance nakon šest meseci bilo značajno veće u grupi bolesnika koji su koristili cilostazol + acetilsalicilnu kiselinu. U podgrupi bolesnika koji su pušili više od 20 cigareta dnevno i duže od 20 godina došlo je do značajnijeg povećanja klaudikacione distance nakon šest meseci u grupi koja je koristila cilostazol + acetilsalicilnu kiselinu u poređenju sa grupom pentoksifilin + acetilsalicilna kiselina. Dakle, broj cigareta na dan i dužina pušenja imaju značajan uticaj na primenjeni terapijski modalitet kod bolesnika sa PAD-om. Terapija cilostazol + acetilsalicilna kiselina bila je efikasnija od terapije pentoksifilin + acetilsalicilna kiselina.

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Ključne reči: *periferna arterijska bolest, lečenje, pušenje*

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FREQUENCY OF MALNUTRITION IN PATIENTS WITH INTRAORAL CARCINOMA

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Malnutrition, or insufficient or poor nutrition, represents a lack of basic nutrients in a human organism. Being incapable of sufficient intake of nutrients, patients with intraoral carcinomas (ICs) are often affected by malnutrition. One of the most frequently used measures of nutritional status is the body mass index (BMI), an anthropometric parameter. When biochemical parameters are concerned, the level of serum albumin (SA) is the one most commonly employed.

The aim of this study was to analyze the nutritional status of patients with IC by measuring the pre-post-treatment values of BMI and SA and to establish the prevalence of malnutrition in these patients.

In the period from 2015 to 2016, we analyzed the patients with the diagnosis of IC treated at the Department of Maxillofacial Surgery, Clinic of Dental Medicine in Niš. The study sample included 20 patients.

The results of our study support the notion that malnutrition in IC patients should be taken into consideration as one of the key factors of treatment success and complete rehabilitation of IC patients. A multidisciplinary approach and use of nutritional support therapy to correct malnutrition have to become an integral part of everyday practice of all clinics dealing with this pathology.

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Key words: *malnutrition, intraoral carcinoma, body mass index, serum albumin*

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Introduction

Malnutrition, or insufficient or poor nutrition, represents a lack of basic nutrients in a human organism. Being incapable of sufficient intake of nutrients, the patients with intraoral carcinomas (ICs) are often affected by malnutrition. One of the elemental tasks of therapists is to recognize malnutrition and to prevent or correct the condition. Malnutrition, by itself, leads to energy and protein deficiencies and aggravates the process of healing and recovery.

Nearly half of patients with IC have a form of malnutrition at the moment of diagnosis, caused by alcohol consumption or dysphagia caused by the neoplastic process itself (1). In addition to the neoplastic process, surgical intervention and postoperative chemoradiation, as the principal treatment algorithm, lead to malnutrition, followed by weight loss and decreased serum albumin level (2). Therefore, in order to prevent post-treatment complications, malnutrition should be taken into account as one of the essential indices. Several studies have examined the impact of pretreatment nutrition status on post-treatment complication rates (3). A large group of available parameters of nutritional status and diversity of grading surgical complications further complicate the understanding of the association between malnutrition and complications in IC patients (1).

One of the most frequently used measures of nutritional status is the body mass index (BMI), an anthropometric parameter. When biochemical parameters are concerned, the level of serum albumin (SA) is the one most commonly employed.

The aim of this study was to analyze the nutritional status of patients with IC by measuring the values of pre-treatment and post-treatment BMI and SA values and establishing the prevalence of malnutrition in these patients.

Material and Methods

In the period of 2 years, we analyzed the patients with the diagnosis of IC treated at the Department of Maxillofacial Surgery, Clinic of Dental Medicine in Niš. The size of the studied

sample was 20 patients. In accordance with the algorithm of the European Association for Cranio Maxillofacial Surgery (EACMFS) for patients with IC, all the studied cases were first treated surgically, followed by adjuvant radiation or chemoradiation therapy. Similar to the paper by Shruti P. et al. (4), the inclusion and exclusion criteria were defined in our study as follows:

Inclusion criteria:

- patients aged above 18 years treated for IC with a histopathological diagnosis of squamous cell carcinoma

Exclusion criteria:

- Patients with distant metastases and T4 disease stage
- Patients who underwent biopsy only, without any surgical treatment
- Patients with oropharyngeal carcinoma
- Patients who did not complete their treatment.

The following information was collected: patient gender, age, localization/site and TNM classification of the disease, height (h) and body mass (bm) of the patients, and serum albumin pre-treatment and post-treatment values.

Based on body mass and height measures, BMI was calculated according to the formula: BMI = kg/m^2, weight in kilograms/height in meters squared, both before and after completion of their treatment.

Some data were presented as frequencies and percentages, while other data were presented as means within intervals.

The average time from the moment of therapy initiation (surgery) to treatment completion (radiation or chemoradiation therapy) was around 4 months.

All the data were collected and presented as tables using MS Office Excell (Microsoft Corp., Redmond, WA, USA), and descriptive statistical analyses were performed using the statistical software package SPSS, version 20.0 (SPSS, Inc., Chicago, IL, USA).

T-test was used to compare the values of BMI and SA before and after treatment; the value of $p < 0.005$ was considered statistically significant. The following information was collected: patient gender, age, localization/site and TNM classification of the disease, height (h) and body mass (bm) of the patients, and serum albumin pre-treatment and post-treatment values.

Based on body mass and height measures, BMI was calculated according to the formula: BMI = kg/m^2, weight in kilograms/height in meters squared, both before and after completion of their treatment.

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T-test was used to compare the values of BMI and SA before and after treatment; the value of $p < 0.005$ was considered statistically significant.

Results

According to the definition by the World Health Organization (WHO), the values of BMI < 20 and SA < 45 g/l were taken to identify the patients with malnutrition.

Basic patient characteristics are shown in Table 1. The patient age range was 32–85 years, 59.4 years on the average. Pre-treatment mean BMI value was 24.25 kg/m^2 (17.44–32.79 kg/m^2) while the corresponding value for SA was 41.85 g/l (31.4–46 g/l). Post-treatment mean BMI value was 21.4 kg/m^2 (16.75–28.38 kg/m^2), while the corresponding value for SA was 39.9 g/l (33.8–49.5 g/l).

As for the nutritional status, 5 patients (25%) were malnourished according to their pre-treatment BMI and SA values; 6 patients (33.3%) were normally nourished; and 9 patients (42%) were obese. According to their post-treatment BMI and SA values, there were 9 patients (45%) with malnutrition; 7 patients (14.5%) were normally nourished; and 4 patients (20%) were obese.

The most common tumor localization was tongue (11 cases; 55%), followed by mouth floor disease (3 cases; 15%). In 4 patients (25%) both localizations were involved.

As for the gender distribution, there was a male-to-female predominance of 15 vs. 5 cases (75% vs. 25%).

According to the TNM classification, most patients had T2 N1 M0 disease—9 patients (45%), while 6 patients had T2 N0 M0 disease (30%).

Post-operative complications were present in all malnourished patients, while among the normally nourished there was 1 such patient (17%), and among the obese, there were 5 patients (58%) with such complications.

During the following time, the values of the BMI were statistically changed between the two measurements ($p < 0001$). The values of SA were not statistically changed between the two measurements $p = 0.193$) (Table 2, Figure 1).

The results of our study confirm that BMI values were statistically reduced in both male ($p = 0.010$) and female patients ($p = 0.026$) in the two measurements. Also, we found that the values of SA were not statistically changed in male patients ($p = 0.639$), but in female patients the SA values were statistically changed in the two measurements ($p = 0.016$) (Table 3, Figure 2).

Table 1. "General characteristics"

Characteristics	Number	%
Age †	59.40 ± 17.11	32–85
Gender		
Male	15	75.0
Female	5	25.0
Localization		
Tongue	11	55.0
Floor of the mouth	3	15.0
Both localization	4	20.0
Classification		
T2	15	75.0
T3	5	25.0
N0	10	50.0
N1	10	50.0
M0	20	100.0

Table 2. BMI and SA values for the two measurements

	First measurement	Second measurement	p[1]
BMI	24.25 ± 4.62	21.40 ± 3.50	0.001
	17.44–32.79	15.19–28.38	
SA	41.85 ± 4.07	39.90 ± 3.92	0.193
	31.40–47.40	33.20–49.50	

[1] T-test: arithmetic mean ± standard deviation

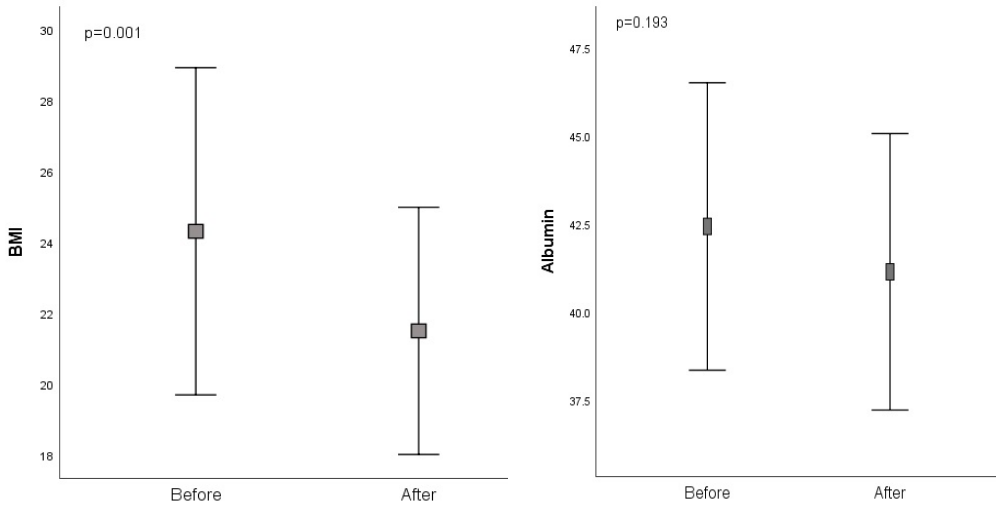

Figure 1. BMI and SA values for the two measurements

Table 3. BMI and SA values for the two measurements concerning gender

		First measurement	Second measurement	p[1]
BMI	Male	23.32 ± 4.39	20.90 ± 3.59	0.010
	Female	27.28 ± 4.37	23.30 ± 2.70	0.026
SA	Male	41.90 ± 4.56	41.33 ± 4.49	0.639
	Female	43.99 ± 1.41	40.58 ± 1.32	0.016

[1] T-test: arithmetic mean ± standard deviation

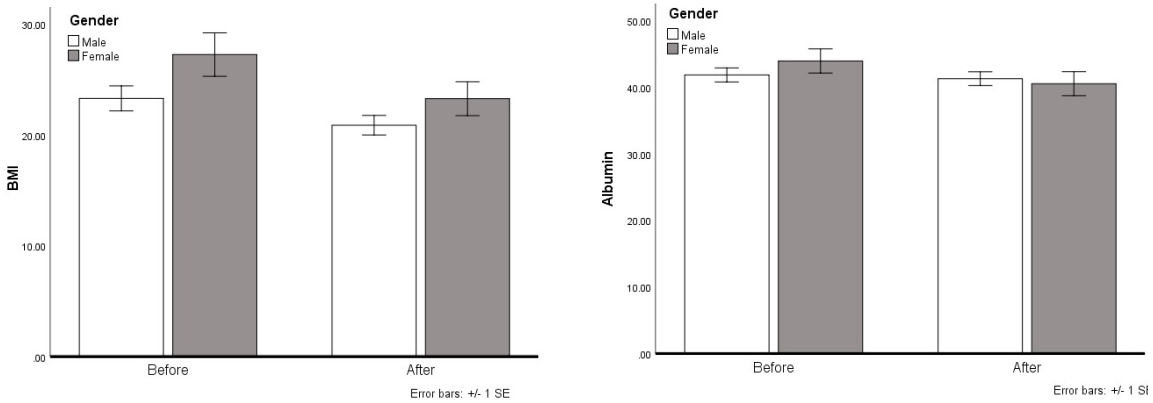

Figure 2. BMI and SA values for two the measurements concerning gender

Discussion

In patients with IC, malnutrition most frequently occurs as the consequence of tumor localization, leading to dysphagia, psychic stress and metabolic changes due to tumor presence and post-treatment complications, as confirmed by the results of a number of studies (1, 5). In the study by Rathod et al., dysphagia has been noted as one of the most common symptoms in patients with IC (6). In the study by Kubrak et al., dysphagia was also identified as the most common cause of malnutrition (7).

Different parameters can be used to define and monitor malnutrition, while in our study BMI was used as an anthropometric and SA as a biochemical parameter. The prevalence of malnutrition was 25% before treatment, and 45% after treatment, which agreed with other studies' results (4). Since there are several methods to establish the nutritional status, there is an unresolved question of their standardization. Nearly all studies agree that in malnourished patients with lower BMI and SA values post-operative complications and longer hospitalization are more common than in normally nourished patients (4, 8). Overall, few studies have investigated the association of malnutrition with post-treatment complications. One of the studies conducted in the Netherlands confirmed that surgically treated patients with a BMI value loss in excess of 10% had a higher probability of complications (4). On the other hand, Matthews et al. could not confirm the association of malnutrition with post-treatment complications and disease stage (9).

The results of our t-test demonstrated a statistically significant difference in p-value between BMI in pre- and post-treatment result groups, but the results of SA demonstrated no statistically significant difference. The values of these parameters in the group of malnourished patients indicated the need for nutritional support prophylactic interventions. Nutritional support therapy is one of the options to remedy malnutrition. Revasco et al. confirmed that malnutrition with body mass loss was more prevalent in the group of patients without supplemental nutritional therapy than in the group receiving such therapy (10). Furthermore, other studies emphasized a positive effect of nutritional support therapy on malnutrition, stressing that such an intervention should be introduced as early as possible (1, 11).

In addition to SA, a systemic inflammation marker, neutrophil/lymphocyte ratio (NLR), is also a haematological parameter associated with malnutrition; it can be a significant indicator of the possibility of occurrence of post-treatment complications in patients with IC (12). Several studies have confirmed the role of NLR as a marker of complications in patients with colorectal carcinoma, cholangiosarcoma and pancreatic carcinoma (13). In the study of Tsai et al. it was shown that this factor had significantly higher values in patients with malnutrition and was not associated with incidence of postoperative complications. In our study, we did not examine NLR values.

In the study by Bao et al. (14), two more nutritional parameters were evaluated: prognostic nutritional index (PNI = albumin + 0.005 x lymphocyte) and nutritional risk index (NRI= 1.519 x albumin + 41.7 x present/ideal body weight). They found that NRI was superior to BMI or SA or PNI. We did not analyse NRI and PNI.

In the study by Peters et al., the factors of age and disease stage have been analyzed. These factors were demonstrated to be significant markers of post-treatment complications (15). The results of our study agree with these findings. On the other hand, Boruk et al. could not demonstrate the association between patient age and post-treatment complications (16). In the study of Linn et al., the association between nutritional status and patient age was analyzed in malnourished and normally nourished patients; it was shown that malnourished and older patients had more complications and greater morbidity than other patients (1). In a large study of 61,740 older IC patients by Genther et al., it was shown that mortality and complications were not associated with more advanced age, but with comorbidities and malnutrition instead (17).

The same findings have been confirmed in some other studies (1). Resulting from the findings of these studies and our own study, preoperative nutritional screening and supportive nutritional therapy represent an essential part of the treatment plan for patients with ICs.

It is necessary to know the nature (type and stage) of the patient's malignancy, the treatment plan (surgical, chemo or radiotherapy), and the expected duration of the disturbance of normal food intake, before starting the nutritional treatment to ensure optimal therapeutic results with minimal morbidity and maximum cost-effectiveness.

The study by Ravasco evaluated nutritional status in cancer patients and found that different cancer types display different nutritional patterns. In clinical practice, oral nutrition is always the first choice. The nutritional plan for every patient should be individualised, and adapted to individual needs (18). Patients with ICs usually have problems with food intake because of tumor localization, and after surgery, they have a nasogastric tube like a normal part of postoperative recovery. In that way, nutritional intake is possible.

The main shortcomings of our study are a relatively small sample (20 patients), a short period of time and the single-centre nature of the study. Furthermore, the study did not involve the patients on supportive nutritional therapy, mentioned in a variety of studies as an effective approach in the prevention and therapy of malnutrition (1, 10, 11), which should be the topic in some of our future studies.

Conclusion

The results of our study support the notion that malnutrition in IC patients should be taken into consideration as one of the key factors of treatment success and complete rehabilitation of IC patients. The obtained results are important for everyday clinical work. A multidisciplinary approach and use of nutritional support therapy to correct malnutrition have to become an integral part of the everyday practice of all clinics dealing with this pathology.

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UČESTALOST MALNUTRICIJE KOD BOLESNIKA SA INTRAORALNIM KARCINOMOM

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Malnutricija ili pothranjenost predstavlja manjak osnovnih hranljivih sastojaka u ljudskom organizmu. Usled nemogućnosti dovoljnog nutritivnog unosa, javlja se kod bolesnika sa intraoralnim karcinomima (IK). Jedan od najčešće korišćenih nutritivnih parametara jeste indeks telesne mase (engl. *body mass index* – BMI), koji spada u antrotopometrijske parametre. Nivo serumskog albumina (SA) najčešće je korišćeni biohemijski parametar.

Cilj ove studije bio je da se analizira nutritivni status bolesnika sa intraoralnim karcinomom, i to merenjem vrednosti pre tretmana i posle tretmana. Analizirani su bolesnici sa dijagnozom intraoralnim karcinomom lečeni na Odeljenju maksilofacijalne hirurgije Klinike za dentalnu medicinu u Nišu u periodu od 2015. do 2016. godine. Istraživanje je obuhvatilo 20 bolesnika.

Rezultati našeg istraživanja govore u prilog tome da se malnutricija kod bolesnika sa IK-om treba razmotriti kao jedan od bitnih faktora uspešnosti tretmana i potpune rehabilitacije bolesnika. Multidisciplinarni pristup i upotreba nutritivne suportivne terapije sa ciljem korekcije malnutricije moraju postati deo svakodnevne prakse svih klinika koje se bave ovom patologijom.

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***Ključne reči**: malnutricija, intraoralni karcinom, indeks telesne mase, serumski albumin*

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RISK FACTORS AND CLUSTER ANALYSIS OF ONYCHOMYCOSIS

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Recently, there has been a trend of identifying different disease phenotypes based on clinical parameters. Cluster analysis is a statistical method for categorizing different clinical signs and symptoms based on how closely associated they are.

The aim of this study was to estimate whether cluster analysis could be used to classify distinct clinical phenotypes of onychomycosis and determine risk factors for this infection.

This prospective study evaluated data from the specially designed questionnaire for superficial fungal infections of the skin and adnexa. The questionnaire was composed of three separate groups of questions, including demographic data, symptoms and clinical signs and risk factors. The hierarchical method of cluster analysis, the Ward method with Euclidian distance, was used in statistical analysis.

The applied statistical method separated patients into two clusters based on clinical presentation. The first cluster consisted of patients with onychomycosis of toenails accompanied by pain, complete destruction of the nail plate, involvement of 2/3 of the nail, and nail thickening greater than 2 mm. The second cluster, consisting of patients with onychomycosis of fingernails, was further divided into two subclusters. The first one included patients with lesions of the nail root, inside of the nail, superficial changes, and infected skin around the nail. The other subcluster included nail plate thickening of up to 1 mm, changes of the free edge, involvement of up to 1/3, and brittleness of the nail. The most common risk factors are obesity (50%), positive family anamnesis (32.0%), nail plate trauma (15.0%), and long-term antibiotic therapy.

Phenotyping the infection and considering it alongside the most prevalent risk factors for onychomycosis can significantly improve predictive assessment and diagnosis.

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Key words: *cluster analysis, onychomycosis, risk factors*

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Introduction

Cluster analysis techniques are often used to identify the pattern of clinical signs and symptom expression, facilitating the definition of more precise diagnostic criteria and categories (1, 2). In recent years, the trend of determining different disease phenotypes based on the grouping of most common symptoms and clinical signs in separate clusters has been growing (3) and is practiced in pulmonology (4), cardiology (5), rheumatology (6), and psychiatry (7). Recently, this statistical method was also used in infectology (8, 9).

Considering the fact that fungal infections, both superficial and invasive, are still being treated empirically based on individual predisposition, symptoms, and signs of the infection, figuring out the phenotypes of these diseases would significantly help in diagnosis. According to available data, one of the fungal infections with an extremely high prevalence, treated without prior laboratory confirmation in more than 60% of cases, is onychomycosis (10). Onychomycosis is a fungal nail disease caused by a dermatophyte, non-dermatophyte molds, or yeasts (11). The most common form of onychomycosis is the distal subungual form, which occurs more often on the toenails (12), although a lateral or proximal subungual form, as well as superficial and endonyx onychomycosis, have also been described (13, 14). All of these forms, if left untreated, can result in total dystrophy of the nail (15–17).

Onychomycosis is often chronic, as the causative agents are often difficult to eradicate, with a tendency to relapse and require treatment with systemic antimycotics (18). In most

laboratories, the diagnostic procedure includes a mycological examination of the patient's material (scarifications and swabs from the site of the change) using a conventional methodology, such as microscopic examination and cultivation. The main disadvantage of mycological analyses is the long duration of the cultivation period and the process of causative agent identification (10). Although designing and establishing fast and accurate diagnostic procedures is of great importance in choosing an appropriate course of treatment, molecular techniques, and point of care, immunochromatographic onychomycosis diagnostic tests are not readily available to most laboratories (10). Therefore, in most cases, onychomycosis is treated empirically based on the clinical signs and symptoms (19). Accordingly, the aim of this study was to determine the most common risk factors for the occurrence of this fungal infection, as well as whether cluster analysis can be applied to classify clinical phenotypes of onychomycosis.

Material and Methods

This prospective study was conducted at the Department of Parasitology and Mycology of the Institute of Public Health in Niš. A specially designed questionnaire for superficial fungal infections of the skin and adnexa was used. The questionnaire was composed of three separate groups of questions. The first group of questions included demographic data, the second group focused on symptoms and clinical findings, and the third was focused on risk factors. The attending physician, a specialist in microbiology, conducted the interview, clinical examination, and questionnaire completion. Data from medical records of 100 patients with laboratory-confirmed onychomycosis (significant finding of fungal elements using microscopic examination (mass of fungal conidia/spores and/or hyphae/mycelial fibers) and isolation of yeasts and/or dermatophyte molds) were included in the study.

This research was carried out in accordance with the principles of the Declaration of Helsinki of 1975 and was approved by the Ethics Committees of the Faculty of Medicine, University of Niš (Decision Number: 12-6316-2/1-2016) and Institute of Public Health in Niš (Decision Number 07-4665/2016).

Statistical analysis

Data are presented as arithmetic mean ± standard deviation, frequency, and percentage. Comparison of different variables between groups was performed by the Mann-Whitney test.

The data analysis was conducted using cluster analysis—the agglomerative hierarchical Ward method, which generated a dendrogram with Euclidean distance. The hypothesis was tested with a significance threshold of $p < 0.05$. Data analysis was performed in the R software package (20).

Results

One hundred patients with onychomycosis were included in the study. Mycotic lesions were more common on the toenails (62.0%) compared to the fingernails (38.0%). Fungal nail disease occurs more often in females (79.0%). The age structure of the examined population was uniform, from 17−79 years (Table 1), and the average age was 45.85 ± 19.61 years. Most of them were from the city (86.0%), and half of the studied population was obese.

The most common pathological changes observed in the studied population were nail deformation (74.0%), raised nail (50.0%), involvement of more than two-thirds of the nail (45.0%), complete alteration of the nail (43.0%), brittle nails (43.0%), pain (37.0%) and disruption of the free edge (32.0%). Other symptoms and clinical signs occurred in less than a third of the examined patients (Table 2).

Cluster analysis included the following parameters: involvement of the free edge of the nail, involvement of the nail root, presence of surface changes, changes inside the nail, complete nail involvement, localization of changes, involvement of up to a half and more than a half of the nail, thickening greater than 2 mm, pain, brittleness of the nail and involvement of the skin around the nail.

Based on the cluster analysis, two clusters were identified. The following symptoms and signs are grouped into the first cluster—lesions of the toenails: a complete change of the nail, more than 2/3 of the nail involved, thickening of the nail greater than 2 mm, and the presence of pain. The second cluster involved fingernail lesions further divided into two sub-clusters (Figure 1). The first one included changes to the fingernail root, inside the nail, nail surface change, and involvement of the skin around the nail. The second sub-cluster contained the following characteristics: thickening of up to 1 mm, disruption of the free edge, involvement of up to 1/3 of the nail, and nail brittleness.

We found that the following risk factors are most common in the studied population: obesity (50% of patients with onychomycosis were with body mass index (BMI) ≥ 25 kg/m^2), positive family history (32%) and existing peripheral vascular disease (11%). The prevalence of other risk factors, each accounting for less than 10% of the examined population, is shown in Figure 2.

Table 1. Demographic and clinical characteristics of the studied population

	Total	
	Number	**%**
Gender		
Male	21	21.0
Female	79	79.0
Age	45.85 ± 19.61	17–79
Age categories		
< 19	10	10.0
20–39	29	29.0
40–59	33	33.0
60–79	28	28.0
BMI*	25.08 ± 4.74	15.83–38.22
Nourishment		
Undernourished < 18.5	9	9.0
Normal 18.5–24.9	41	41.0
Obese > 25.0	50	50.0
Place of residence		
The countryside	14	14.0
City	86	86.0

* BMI—body mass index; people with BMI < 18,525 kg/m^2 are considered undernourished; BMI from 18.525 to 24.9 kg/m^2 counts as normal body mass, and obese are with BMI ≥ 25 kg/m^2.

Table 2. Clinical signs and symptoms in the studied population

Clinical signs and symptoms	Total*
Deformation of the nail	74
Raised nail	50
More than 2/3 of the nail involved	45
Nail plate thickening >2 mm	45
Complete nail alteration	43
Brittle nails	43
Pain	37
Disruption of the free edge	32
Less than 1/3 of the nail involved	26
No thickening or less than 1 mm	26
Affected skin around the nail	24
Nail involvement of 1/3 up to 2/3	23
Nail plate thickening 1–2 mm	23
Surface changes	11
Changes inside the nail	11
Alterations of the nail root	7

* Prevalence percentage of the corresponding clinical sign or symptom

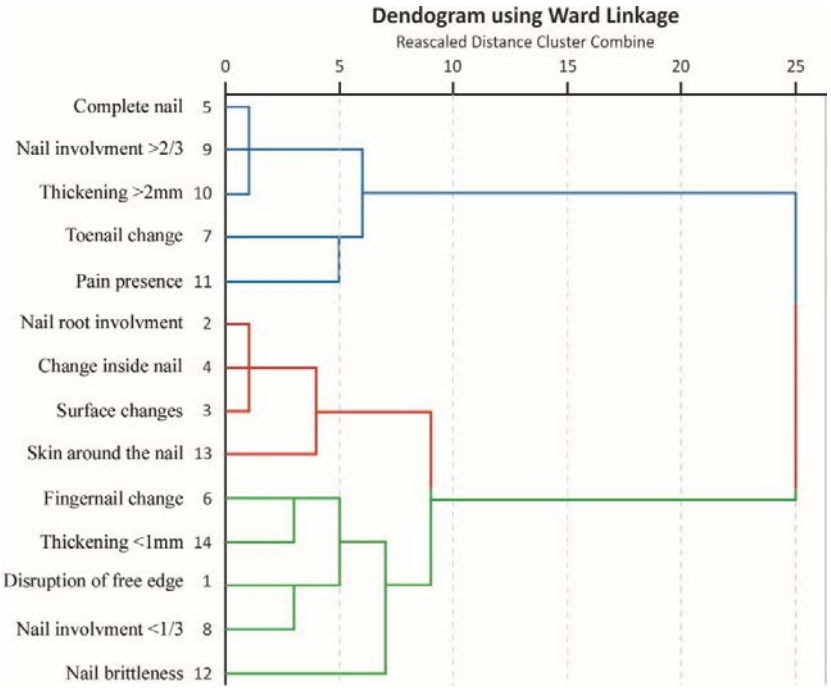

Figure 1. Cluster analysis of symptoms in patients with onychomycosis

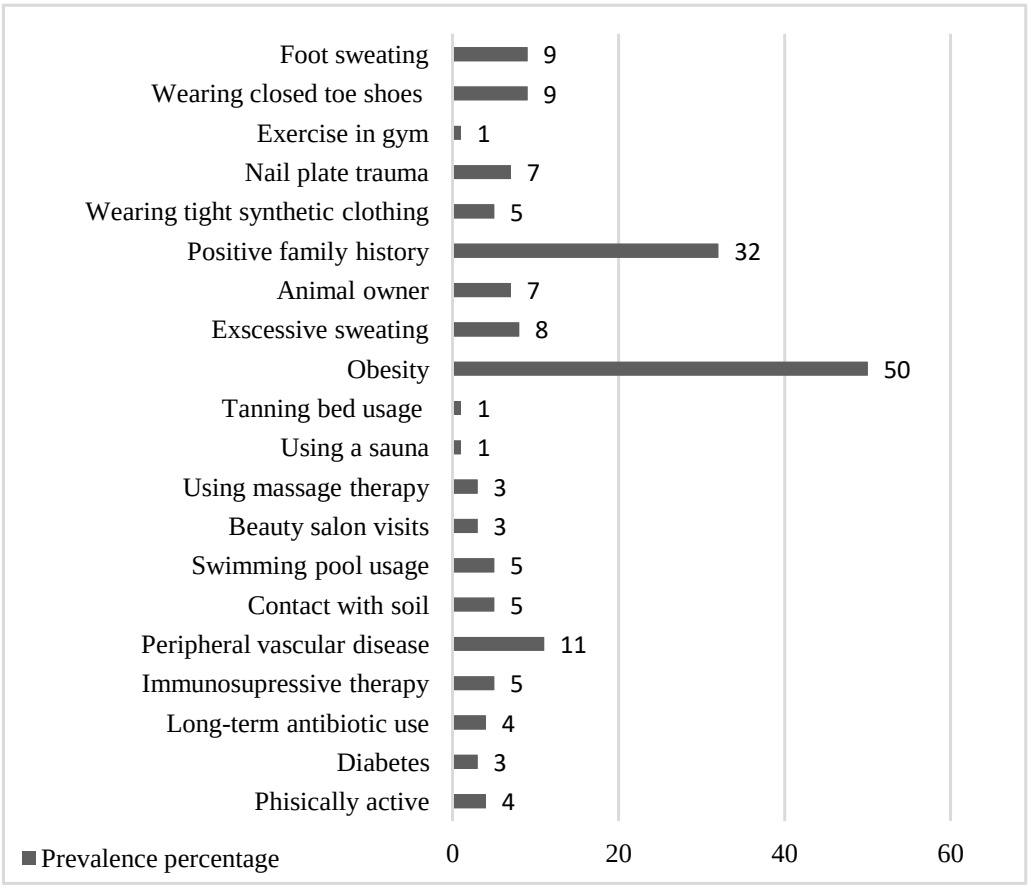

Figure 2. Distribution of risk factors in the examined population

Discussion

All observed signs and symptoms in the studied population are characteristic of onychomycosis (21, 22). However, numerous manifestations of fungal infections can also be found in other diseases (23), so they must be taken cautiously and interpreted in accordance with the complete clinical presentation, predisposing factors, and, in the best case, after a laboratory, mycological examination. Empirical treatment of onychomycosis, the duration of mycological analysis to confirm the fungal infection in the laboratory, as well as the wide range of different symptoms and signs by which onychomycosis manifests, indicate the need to separate these infections into different phenotypes, to be able to set an accurate diagnosis easier.

The cluster analysis can be used to associate clinical manifestations that occur together to achieve this separation of the different phenotypes. For this purpose, the hierarchical cluster analysis method can be used. It begins with one cluster and then gradually combines variables to form the smallest number of clusters with the greatest similarity of variables within clusters and the greatest dissimilarity between them.

Namely, this statistical method is increasingly used in diseases that can present with numerous various symptoms and signs. For example, it is used to classify and group symptoms in chronic diseases, especially in oncology (24, 25). On the other hand, this type of analysis is rare in the case of infectious diseases. So far, this statistical method for determining phenotypes of manifest infection with laboratory evidence has been used in cases of vulvovaginal candidosis and Aspergillus-otomycosis (8, 9). However, this paper represents one of the first studies of cluster analysis of nail fungal infection.

The hierarchical method of cluster analysis in this study shows the first differentiation of toe-onychomycosis and fingernail-onychomycosis as two clusters. Interestingly, the cluster of fingernail onychomycosis also contains two additional subclusters. That is, the analysis of the results indicated the existence of one phenotype of onychomycosis of the toenails and two phenotypes of fingernail onychomycosis.

Toenail phenotype includes the presence of the infection on the toes, with complete alteration or involvement of two-thirds of the toenail, thickening of the nail greater than 2 mm, and the presence of pain. Fingernail phenotype encompassed two different sub-phenotypes of the fungal infection. The first one was manifested by the changes in the nail root and endonyx (lesions within the nail plate, surface changes, and involvement of the skin around the nail). In addition, there was a second subcluster within the fingernail onychomycosis group, which included signs such as nail thickening of up to 1 mm, alterations on the distal part of the nail plate, i.e., on the free edge, brittleness, and involvement of up to one-third of the nail.

Analyses of the identified phenotypes indicate a clear grouping of signs of more extensive infection and pain with mycotic lesions of the toenails. Contrary to that, in the case of onychomycosis of the fingernails, signs of the infection are more discrete.

One of the techniques used to determine cluster diversity is the visual observation of graphic displays or dendrograms. Although the dendrogram clearly clustered signs and symptoms into three phenotypes, the possible overlap between variables, particularly between neighbouring clusters, should be highlighted. For the first cluster, the involvement of the nail root can additionally be considered. For the second cluster, the pain presence can be considered. Consecutively, for the third cluster, the presence of skin changes around the nail might be assumed.

Even though the dendrogram construction is one of the critical steps in this type of statistical analysis since every step in the formation of clusters can be visually observed, its interpretation requires caution (21). The major drawback of applying this type of analysis is that different cluster analysis techniques can produce different results. Therefore, it is recommended that cluster analysis should be followed by principal component analysis. In this two-way process, the validity and reliability of the data can be verified with greater confidence (22).

As for risk factors, obesity, positive family history and trauma to the nail plate were most often noted among the examinees. Other authors usually associate these factors with onychomycosis (22, 26). Additionally, long-term use of antibiotics was found in 11%, and diabetes mellitus in less than 10% of our respondents (27). The sporadic presence of these risk factors among those examined can be explained by the severity of the underlying diseases, leading to onychomycosis being neglected and not confirmed by laboratory tests. Phenotyping the infection and considering it together with the risk factors most commonly present in onychomycosis can significantly aid in predictive assessment and diagnosis.

Conclusion

Even though statistical methods are relatively complex, identifying different clusters of onychomycosis's clinical characteristics would significantly contribute to a better understanding of the disease and an adequate assessment of the patients. Our study showed that cluster analysis could be useful in identifying phenotypes of symptoms and signs of nail fungal infections. However, further research is needed to estimate an association between clusters of symptoms and signs and type of causative agent of fungal nail infection, as well as a comparison between phenotypes of onychomycosis with phenotypes of other nail diseases.

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FAKTORI RIZIKA ZA POJAVU ONIHOMIKOZA I KLASTER ANALIZA

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Definisanje različitih fenotipova bolesti na osnovu kliničkih parametara predstavlja trend u istraživanjima sprovedenim poslednjih godina. Klaster analiza je statistička metoda za kategorizaciju različitih kliničkih znakova i simptoma na osnovu stepena njihove povezanosti.

Ovaj rad je za cilj imao da ispita mogućnost primene klaster analize za klasifikaciju različitih kliničkih fenotipova onihomikoze i određivanje faktora rizika za nastanak ove infekcije.

U ovoj prospektivnoj studiji korišćeni su podaci dobijeni posebno dizajniranim upitnikom u vezi sa površinskim gljivičnim infekcijama kože i adneksa. Upitnik se sastojao od tri grupe pitanja, koje su obuhvatale demografske podatke, simptome i kliničke znake, kao i faktore rizika. U statističkoj obradi podataka korišćena je hijerarhijska metoda klaster analize, Vordova metoda sa euklidskom distancom.

Primenjenom statističkom metodom bolesnici su podeljeni u dva klastera. Prvi klaster činili su bolesnici sa onihomikozom noktiju na stopalima, praćenom bolom, potpunim uništenjem nokatne ploče, zahvaćenošću 2/3 nokta i zadebljanjem nokta većim od 2 mm. Drugi klaster koji su činili bolesnici sa onihomikozom noktiju na šakama, dalje je podeljen na dva potklastera. Prvi je uključivao bolesnike sa lezijama korena nokta, unutrašnjosti nokta, površinskim promenama i zahvaćenom kožom oko nokta. Drugi potklaster obuhvatao je bolesnike kod kojih su uočeni zadebljanje nokatne ploče do 1 mm, promene slobodne ivice, zahvaćenost do 1/3 nokta i lomljivost nokta. Utvrđeno je da su najčešći faktori rizika bili gojaznost (50%), pozitivna porodična anamneza (32,0%), trauma nokatne ploče (15,0%) i dugotrajna terapija antibioticima (11,0%).

Fenotipizacija infekcije i njeno razmatranje uz najzastupljenije faktore rizika za onihomikozu mogu u velikoj meri poboljšati procenu i dijagnozu bolesti.

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***Ključne reči**: klaster analiza, onihomikoza, faktori rizika*

Original article

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MULTIMODAL REHABILITATION TREATMENT OF PATIENTS WITH SCIATICA

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Pain radiating from the lower back to the lower limb below the knee is known as sciatica. The purpose of this research was to ascertain how patients with sciatica responded to multimodal rehabilitation therapy.

Fifty-one patients with persistent sciatica receiving treatment at the Medical Rehabilitation Clinic of the Clinical Center of Vojvodina were included in the study. In addition to demographic information, we also collected scores from the Oswestry Disability Index, Central Sensitization Inventory, Fear Avoidance Component Scale, and Numerical Rating Scale. At the beginning and completion of the treatment, results were acquired.

Thirty-four out of the patients, or 66.7%, were female. The stationary multimodal treatment for chronic pain took place for a period of 20.48 ± 5.89 days. After the treatment, the NRS assessed pain intensity had significantly decreased (6.49 ± 2.22 vs. 5.00 ± 2.22, $t = 5.629$, $p < 0.001$). Following the treatment, there was a substantial improvement in the average ODI score (48.75 ± 15.16 vs. 42.24 ± 14.13 ($t = 4.246$, $p < 0.001$) and FACS score (66.80 ± 14.13 vs. 62.47 ± 16.49, $t = 2.086$, $p = 0.042$). After the course of the treatment, the CSI score decreased, although this change was not statistically significant ($t = 1.446$, $p = 0.155$).

Patients receiving stationary comprehensive rehabilitation treatment see improvements in their functional status, a decrease in their level of fear-induced activity avoidance, and a reduction in the severity of their pain.

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Key words: *chronic sciatica, disability, the pain, multidisciplinary treatment*

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Introduction

Sciatica is a pain that spreads from the lower back to one or both lower extremities to below the knee. Usually, sciatica is caused by nerve root compression. Neuroradiological studies confirm that 85% of sciatica cases are related to intervertebral disc disorders (1). The most commonly affected are the L5 and S1 nerve roots, somewhat less often the L4 nerve roots (2).

However, there are other possible causes of sciatica, such as traumatic injury of the sciatic nerve, muscle hematomas, tumors, piriformis syndrome and myofascial pain syndrome (3–6).

Treatment of sciatica presents a major challenge for medical professionals and the health care system in general (7). Current approaches recognize the value of a multimodal treatment that focuses not only on nociceptive aspects of pain but also on cognitive-evaluative and motivational-affective aspects (8). Evidence-based multimodal treatment of sciatica represents a significant advance in the treatment of this condition (9, 10). Multimodal treatment consists of a combination of pharmacological and non-pharmacological therapy, which includes the use of physical therapy, psychological and cognitive-behavioral therapy. A multimodal approach more adequately and comprehensively manages pain at the molecular, behavioral, cognitive and functional levels (11). These approaches have been shown to lead to superior and long-lasting outcomes, including pain perception, mood, restoration of physical functioning, work status and medication use (8).

Pharmacological therapy begins after an accurate diagnosis. A key component of drug pain management is finding a balance between desired effects and acceptable side effects. Long-term use of painkillers in the treatment of sciatica may be associated with unpredictable efficacy, reduced tolerance to drug effects, and potentially more serious side effects (3, 12).

In the case of non-pharmacological therapy the importance of physical medicine and

rehabilitation, which contributes to the improvement and maintenance of physical functioning and a better quality of life of the patient, is particularly emphasized. Physical therapy mainly focuses on kinesitherapy and electrotherapy modalities. Electrotherapy procedures in sciatica are primarily intended to reduce the intensity of pain, relax muscle spasms, prevent muscle atrophy, increase local blood circulation, as well as maintain and increase range of motion (13).

Clinical guidelines recommend the provision of 'encouragement to stay physically active'. Moreover, bed rest is not recommended (14). Physical activity is a key element in the treatment of chronic pain conditions. Various types of exercise have been proven to reduce pain, improve physical functioning and quality of life in patients with chronic pain. The use of aerobic exercises has positive effects on pain modulation, nutrition of the intervertebral disc and the mechanics of the spinal column itself (15). Great attention is paid to hydrokinesitherapy, because water, with its mechanical and thermal properties, has a beneficial effect on the musculoskeletal system (16).

In addition to reducing the perception of pain, exercise has an impact on mental health, improves mood, and reduces stress and depression that are often associated with chronic pain conditions (17, 18).

The aim of this study was to determine the effect of multimodal rehabilitation treatment on patients with sciatica.

Material and methods

The research was designed as a prospective case study, conducted at the Medical Rehabilitation Clinic of the University Clinical Centre of Vojvodina and included patients who were treated between September 1st and December 1st, 2018 for chronic sciatica.

Chronic sciatica is defined as pain in the lower back that spreads to one or both lower extremities below the knee level for more than six months.

Inpatient multimodal treatment consisted of drug treatment and physical therapy. Drug therapy was prescribed by the physician in charge of the patient's treatment. Physical treatment consisted of therapeutic exercises that were routinely carried out at the Medical Rehabilitation Clinic (exercises to increase muscle strength, improve balance and coordination, increase flexibility and muscle tone), therapeutic modalities (interfering currents, magnetotherapy, laser therapy, sonophoresis, etc.), hydrotherapy and ergonomic education of patients.

In the present study, 51 patients were included in the research. The criteria for inclusion in the research were the presence of sciatica, and the age of the subjects (18 years and older). Criteria for exclusion from the study: subjects under 18 years of age, presence of malignant disease, pain that lasted less than 3 months, patients who had spine surgery in the last 6 months, and patients who did not understand the Serbian language. The study was approved by the Ethics Committee of the University Clinical Center of Vojvodina (No 00-28/864).

We obtained data on age, gender, level of education, duration of pain, and duration of inpatient multimodal treatment. In addition to these data, patients filled out a set of questionnaires given hereinafter.

The Serbian version of the Central Sensitization Inventory (CSI-Serb) designed to show that the symptoms experienced by the patient were related to the central sensitization syndrome. It consists of two parts. Section A provided 25 items related to central sensitization syndrome with a score from 0 to 100. Each item carried a 5-point Likert scale from 0 (never) to 4 (always). Based on section B through 7 questions (not numbered), we learnt about the patient's previous diagnoses (restless legs syndrome, chronic fatigue syndrome, fibromyalgia, temporomandibular dysfunction, migraines, irritable bowel syndrome, neck injuries, anxiety and depression) (19–21).

The Serbian version of the Fear Avoidance Component Scale (FACS-Serb), consisted of 20 items to which the respondent answered on a six-point Likert scale from 0 (completely disagree) to 5 (completely agree). The FACS-Serb score can range from 0 to 100, where a higher score indicates a greater degree of activity avoidance (22).

The Oswestry Disability Index (ODI) was used to assess the functional status of patients with the lumbar syndrome. There were 10 items to which the respondents answered on a six-point Likert scale from 0 to 5, where 5 indicates the greatest level of activity limitation. The index is expressed in percentages, and a higher value of this index represents a greater degree of limitation in activities of daily life (12, 13).

Pain intensity values were collected according to the Numerical Rating Scale (NRS). We examined current pain (at the time of the survey), maximum pain in the past 4 weeks, and average pain intensity in the past 4 weeks. The scale consisted of 11 items ranging from 0 (no pain) to 10 (worst possible pain) (23).

The data were processed with the statistical program SPSS 23 for Windows. Descriptive and inferential statistics methods were used during the statistical data processing. Comparison of numerical data from different groups was performed using parametric and non-parametric methods. Student's t-test of paired samples was used, and categorical data were analyzed using Chi-square. A value of $p \leq 0.05$ was taken as significant.

Results

The present study included 51 participants; the majority were women (34; 66.7%). The average age of the subjects was 54.55 ± 14.74 years. The youngest patient was 21 years old, while the oldest patient was 80 years old.

The largest number of respondents had a secondary level of education (33; 64.7%), and the smallest number of them had a tertiary education (3; 5.9%).

Patients reported that the pain lasted an average of 55.65 months, while the duration of inpatient multimodal chronic pain treatment at the Medical Rehabilitation Clinic lasted an average of 20.47 days (Table 1).

Table 2 shows the scores of the Central Sensitization Inventory (CSI-Serb), the Oswestry Disability Index (ODI), the Fear-Avoidance Scale (FACS-Serb), as well as pain intensity before and after multimodal treatment. Functional status determined on the basis of ODI ($t = 4.246$, $p < 0.001$, FACS-Serb scores ($t = 2.086$, $p = 0.042$), as well as pain intensity ($t = 5.629$, $p = < 0.001$) significantly improved after multimodal treatment at the Medical Rehabilitation Clinic.

The degree of central sensitization symptoms determined on the basis of the CSI-Serb improved after the treatment, but this difference did not reach statistical significance ($t = 1.446$, $p = 0.155$).

Table 1. Sample characteristics

	Mean	SD
Age (years)	54.55	± 14.74
Sex (female %)	34 (66.7%)	
Duration of pain (months)	55.65	± 92.85
Duration of the treatment (days)	20.47	± 5.89

Table 2. Comparison of questionnaire results before and after treatment

	BEFORE TREATMENT		AFTER TREATMENT		t	p
	Mean	SD	Mean	SD		
CSI-Serb[1]	38.39	11.97	35.84	15.05	1.446	0155
ODI[2]	48.75	15.16	42.24	14.13	4.246	< 0.001
FACS-Serb[3]	66.80	14.13	62.47	16.94	2.086	0.042
NRS[4]	6.49	2.22	5.00	2.22	5.629	< 0.001

[1] Central Sensitization Inventory
[2] Oswestry Disability Index
[3] Fear Avoidance Component Scale
[4] Numerical Rating Scale

Discussion

Chronic sciatica is one of the most common pain syndromes in developed countries (15).

Multimodal treatment is defined as the simultaneous use of two or more different therapeutic treatments with different mechanisms of action with a common goal (24). At the Medical Rehabilitation Clinic, multimodal treatment consists of therapeutic exercises, therapeutic modalities, hydrotherapy, and patients also receive drug therapy. Unlike most similar treatments in developed countries, the treatment does not include psychotherapy, so the interpretation of the results is particularly interesting from this aspect.

The Central Sensitization Inventory is a reliable, valid scale for examining the presence of symptoms of central sensitization (25–30). In our study, an improvement in the CSI score after treatment was shown, but the difference we obtained was not statistically significant. Although there was some indication that the CSI could be used as a tool to monitor the effect of treatment (16), we failed to show that it was significantly different at the beginning and the end of the treatment. There are probably more reasons for these results. First, it is possible that the CSI is not a suitable instrument for monitoring the effect of multimodal treatment, which in our case was without psychotherapy. Another potential reason could be that CSI is not sensitive enough to detect changes occurring in such a short time interval. In any case, it is necessary to further examine changes in the CSI score in relation to potential treatments, as well as in follow-up studies to determine whether this scale has the potential to be used as a tool to assess the effectiveness of chronic pain treatment (31, 32).

The Oswestry index is often used to assess the functionality of patients with lumbar syndrome (33, 34). Inpatient multimodal treatment resulted in a significant improvement in the functionality of patients determined on the basis of the ODI. Other authors also found similar improvements after multimodal treatment (35, 36). Some authors find that there is a significant improvement, in up to 73% of examined patients with chronic sciatica, after physiotherapeutic treatment (27). Although there are significant differences in the content of multimodal treatments, most include psychotherapy (37–39). There are also those who examined the influence of therapeutic exercises (40–42), which was the most similar to our study, so we can assume that in patients with chronic sciatica, therapeutic exercises are very important for functional improvement.

We should not lose sight of the fact that a significant number of patients with sciatica have a pronounced neuropathic pain component for which they received specific therapy during inpatient treatment, which could also significantly contribute to the functional improvement of these patients (43, 44).

Avoidance of activity due to fear is very common in patients with chronic pain (45). The Fear avoidance component scale (FACS) developed by Neblet et al. (2016) has been shown to be a potentially useful tool for assessing this phenomenon (25). Our results showed that there was a significant improvement in the FACS score, and thus a reduction in the severity of this phenomenon after multimodal treatment at the Medical Rehabilitation Clinic. Other authors also observed after treatment a reduction in the level of fear of activity in patients with sciatica that lasted up to 6 months (46). The observed improvement can be attributed to the fact that during the multimodal treatment, there was communication with healthcare workers (doctors, physiotherapists, nurses, psychologists), and even patients, which certainly had a "psychotherapeutic" effect. This kind of interaction certainly helped to reduce the fears and doubts they had, which significantly contributed to the phenomenon of avoiding activities due to fear. In a certain sense, this type of communication can be seen as a form of patient education and as such has positive effects in patients with a high level of activity avoidance due to fear (47).

In the work of Childs et al., 82% sciatica patients experienced a decrease in pain intensity after a four-week treatment, as measured by the Numerical Pain Scale (48). In our study, positive treatment effects were also observed. This scale showed the best results compared to the other scales, supporting the conclusion that the multimodal treatment according to these criteria was successful (49). It could be said that, in addition to the previously mentioned improvements, it was expected that there would also be a decrease in the intensity of pain on the NRS as the most obvious result in the treatment of pain.

The possibility that patients may feel a certain "pressure" from healthcare workers, when assessing the intensity of pain after treatment, should not be excluded. They may state that the treatment had a more favorable outcome and that the intensity of the pain was reduced more than it was, in order to justify the "effort" that went into their treatment. In our study, although some patients were interested in the values of the first measurement taken, they did not have the opportunity to know the intensity of the pain they had reported at the beginning. We must not ignore the fact that the relationship between the healthcare professional and the patient can influence the obtained values and potentially represent a source of error.

Conclusion

Inpatient multimodal rehabilitation treatment for sciatica patients leads to an improvement in functional status, a reduction in the level of activity avoidance due to fear and a reduction in pain intensity.

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MULTIMODALNI REHABILITACIONI TRETMAN BOLESNIKA SA LUMBOIŠIJALGIJOM

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Lumboišijalgija se definiše kao bol u donjem delu leđa sa propagacijom u donji ekstremitet ispod nivoa kolena. Podaci o najefikasnijem lečenju ovog stanja su oskudni. Stoga, cilj ovog istraživanja bio da se ispita efikasnost multimodalnog rehabilitacionog tretmana kod bolesnika sa lumboišijalgijom.

Pedeset jedan (51) ispitanik sa hroničnom lumboišijalgijom lečen je na Klinici za medicinsku rehabilitaciju Kliničkog centra Vojvodine. Uz demografske podatke, na početku i na kraju tretmana praćene su vrednosti Numeričke skale bola (engl. *Numerical Rating Scale* – NRS), Osvestrijevog indeksa onesposobljenosti (engl. *The Oswestry Disability Index* – ODI), vrednosti Skale centralne senzitizacije (engl. *Central Sensitization Inventory* – CSI) i vrednosti Skale izbegavanja aktivnosti usled straha (engl. *Fear Avoidance Component Scale* – FACS).

Veći broj ispitanika činile su žene (34; 66,7%). Stacionarni multimodalni tretman hroničnog bola trajao je 20,48 ± 5,89 dana. Rezultati intenzitet bola po NRS-u bili su značajno manji nakon tretmana (6,49 ± 2,22 prema 5,00 ± 2,22; t = 5,629, p < 0,001). Prosečna vrednost ODI (48,75 ± 15,16 prema 42,24 ± 14,13; t = 4,246, p < 0,001) i prosečna vrednost FACS-a (66,80 ± 14,13 prema 62,47 ± 16,49; t = 2,086, p = 0,042) nakon tretmana ukazivale su na značajno poboljšanje. To nije bio slučaj sa CSI skorom – tu nije bilo statistički značajne razlike nakon multimodalnog tretmana (38,39 ± 11,97 prema 35,84 ± 15,05; t = 1,446, p = 0,155).

Primenom multimodalnog stacionarnog rehabilitacionog tretmana postiže se poboljšanje funkcionalnog statusa, smanjenje intenziteta bola, kao i smanjenje stepena izbegavanja aktivnosti usled straha kod bolesnika sa hroničnom lumboišijalgijom.

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***Ključne reči**: lumboišijalgija, onesposobljenost, bol, multimodalni tretman*

Original article

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FACTORS DETERMINING QUALITY OF LIFE IN THE OPIATE ADDICTS POPULATION

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It is possible that gaining an understanding of the factors that influence the quality of life of opiate addicts may improve both the quality of therapy and its overall effectiveness. There is a correlation between the many treatment facets and overall healthcare attributes, which results in a variable quality of life. In addition to the characteristics of the addiction, other aspects of the addict's life, such as demographics, socioeconomic status, and health, may also have an impact on the addict's quality of life. The purpose of this research is to determine whether or not certain characteristics of addicts, addiction, and treatment have a predictive influence on the quality of life of opiate addicts who were treated using the two approaches that are the most common.

Epidemiological cross-sectional research was performed in 2020 on a random sample of 70 opiate addicts treated at University Clinical Center Niš (35 addicts in the methadone maintenance program and 35 addicts treated with buprenorphine). Using standardized World Health Organization (WHO) instruments for measuring health status (EQ-5D), severity of addiction consequences (ASI), and quality of life (WHOQOL), the necessary data were collected through "face-to-face" interviews with respondents based on an independently developed questionnaire, from which health indices were calculated (EQ-5D Index), severity of addiction consequences (Addiction Severity Index), and quality of life (WHOQOL-BREF Index). The data were presented using appropriate descriptive statistics techniques, and group differences were evaluated using the χ^2 test (Chi-squared test) and t-test. Using multiple regression and correlation, predictors were extracted.

In terms of the quality of life index values, there was no significant difference between addicts who were treated with methadone and addicts who were not treated with methadone. However, the former reported experiencing a much worse quality of life compared to the latter. Health traits, characteristics of respondents' socioeconomic positions, and other addiction-related outcomes were the most prominent factors in the degree to which one's quality of life was affected. The effects of the treatment were becoming less noticeable. Methadone treatment had a predictive influence on the addict's outlook on life as well as the addict's degree of satisfaction with both their psychological state and their surrounding environment. The duration of methadone therapy as well as any breaks in care were the two most important indicators. The consequences of methadone therapy on both the body and society were, on the whole, rather mild.

It is impossible for a single predictor to account for variations in both the degree and the perception of quality of life across a number of different aspects. The number of aspects that are considered is rather high, and the implications that follow from this are complex.

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Key words: *opiate addicts, treatment, quality of life, predictors*

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Introduction

The quality of life of methadone-treated addicts is always poorer than that of healthy individuals or the general population, according to all measurements (1). In contrast, there is no consensus about the comparability of methadone-treated and untreated addicts' quality of life. In addition, several studies highlight the negative effects of methadone treatment on various elements of quality of life.

Although there is unanimity on the efficacy of methadone therapy, the quality of life of addicts undergoing this treatment varies across dimensions. Variations are often associated with varying treatment parameters (duration, dose strength, therapeutic content, psychological

support) and general healthcare features. Variations in the quality of life of methadone-treated opiate addicts are, however, also associated with demographic, socioeconomic, health, and addiction characteristics.

It is difficult to discern between the effects of demographic characteristics and other factors on the quality of life of addicts (1). Guillery, Zielinski (1, 2) and Bawor (3) emphasise that the effects of gender-specific characteristics must be examined alongside the impact of job, family structure, and living environment. Lin (4) establishes a predictive influence of age on the quality of life of addicts in the physical domain but cautions that it must be evaluated in conjunction with other variables such as employment, comorbidity, hospitalizations, usage, and age at initiation of drug use. Huissoud (5) confirmed these findings, mostly in younger addicts. Unidentified is the influence of age on the psychological domain of quality of life.

One of the factors significantly predicting the quality of life of addicts (1, 2, 4, 6) is their socioeconomic level, which is composed of multiple components. Sanders (7) emphasises the necessity of education. It may be considered a predictor of improvements in the psychological and social areas of quality of life, but its influence on the physical domain is negligible. According to Peack (6), employed patients have substantially greater psychological and social functioning. Guillerry and Lin (1, 4) connect employment to enhanced performance in males but to physical improvement and worsening environmental circumstances in females.

It is difficult to determine the effect of the environment on variations in the quality of life of addicts participating in the methadone programme as it is often mediated by numerous other personal variables, drug-related and/or treatment-related factors. Aghayan (8) attributes variations in quality of life to the influence of living situation, financial situation, and participation in free andsocial activities, as opposed to the direct influence of heroin, and identifies the inability of addicts to adapt to new life circumstances as the most significant predictor of low quality of life. Huissoud (5) emphasises the importance of substandard living conditions and lack of permanent residence as predictors of a poor quality of life for addicts. Others, such Guillerry (1), Aghayan (8), Lin (4), and Tracy (9), emphasise the importance of family, home, and relationships inside the home. Tracy (9) reveals that childbearing women have a decline in social support, psychological and environmental domains, and execution domains. Tracy (9) highlights the importance of living environment and social support, the impacts of which are amplified in the presence of symptoms and trauma (violence against women). According to De Maeyer (10), the support of family members during recovery and the support of friends during abstinence are consistently related to the quality of life in all four domains. De Maeyer also emphasises the significance of psychosocial maladaptation, especially the inability to change one's own life situation. Under such conditions, the presence of at least one exceptional buddy and planned daily activities may have a substantial and positive impact on life quality. Additionally, Lin corroborated the effect of emotional, physical, and sexual abuse on differences in psychological domain life quality (4). De Maeyer (10) observed that the existence of a social network and close friends prepared to give aid to the addict had a protective effect. Providing social aid to addicts influences their quality of life (11).

The health characteristics of addicts significantly impact their quality of life. In this context, the influence of comorbidities, chronic diseases, psychological distress, depression, and HIV infection on disparities in quality of life across particular groups is highlighted (12).

According to Tracy (9), the prevalence of symptoms and trauma may explain inequalities in quality, especially in the physical and psychological domains. Alcohol usage (amount drank during the past 30 days) may explain variations in the environment domain. According to De Maeyer (8), the level of psychological distress and the usage of psychotropic medicines are related to a poor quality of life. According to Wang (12), HIV+ patients received significantly worse quality of life ratings in the areas of physical health and functional abilities, as well as in the domain of overall health-related quality of life.

Widespread consensus exists that the addict's addiction features (drug type, quantity of abused substances, their combination, duration of drug addiction, and frequency of drug use) have a significant influence on the addict's current quality of life and expected changes. Bawor (3) discovered that there are differences in the results of male and female addicts, which may be ascribed to the idiosyncrasies of opioid use and initial treatment characteristics. Lin (4) observed that age at first drug use (injection episode) was significantly correlated with quality of life in the physical domain. Abuse of sedatives, cocaine use, duration of cocaine use, and use of a large number of substances in the previous month are all significantly associated with the psychological domain of quality of life. Nevertheless, they all concur that disparities in the physical and psychological aspects of quality of life cannot be solely explained by pharmaceutical effects. According to De Maeyer (13), heroin use has no direct effect on life quality. In addition to other (personal and environmental) elements, drugs have an effect (life situation, financial situation, changes, perspective, participation in free and social activities, support of the environment).

Numerous research have investigated the effect of therapy on the quality of life of opiate addicts. Feelemayer (14), reporting the results of a meta-analysis, asserts that opioid substitution therapy may increase the quality of life and lower

the ASI index among treatment patients over time, but fails to explain the causes of these improvements. When researching the effect of methadone treatment on drug users' quality of life, De Maeyer (10,13) observed statistically significant changes in the WHOQOL-BREF index across all four domains. Prior to enrolling in a treatment programme, the addict's quality of life is a significant predictor of early quality of life improvement and longer retention in the methadone maintenance programme. Dehghan (15) discovered that individuals with a worse health-related quality of life before commencing treatment saw a greater increase in quality of life throughout the first six months of therapy. Only the quality of life before treatment and its early changes are statistically significantly associated with a minimum treatment length of six months. Others (14, 5) identify the first treatment as an indication of poor programme retention. The length of treatment has an impact on life quality. Some research contends that the quality of life diminishes with time (4, 8, 10), whilst others claim the opposite (16-19). The majority of research agrees that the advantages of methadone treatment are greatest in the first three months (20, 21), while the programme continues to have some (positive) effects thereafter. However, methadone maintenance does not affect all facets of life quality in the same manner. Various studies have shown that methadone treatment is more beneficial in the psychological domain (20), the physical and social domains (21), and the physical, psychological, and environmental domains (22, 23, 24). A negligible number of studies demonstrate a significant improvement in all four categories of quality of life (24, 25). Whether the treatment is based on methadone or buprenorphine, Sacerdote (26) and Marinković (27) found that significant improvements in quality of life may be gained. There is no statistically significant association between the length of methadone maintenance and quality of life, according to some researchers (17). In addition, there is no consensus on the dose of methadone. While some claim that a higher dose of methadone has a significantly greater potential to improve quality of life and reduce the number of unmarried occurrences during treatment (5, 28), others emphasize that the dosage of pharmacological medications cannot be correlated with quality of life improvements (18).

The existence of a substantial positive correlation between the quality of life in the physical, psychological, and social domains, and the importance of the intermediate outcomes, demonstrates that the development of any component may influence other elements of health, i.e., quality of life (6). Not only is continuous, uninterrupted treatment statistically associated with drug abstinence, but it is also the strongest predictor of changes in quality of life (5, 6). Significantly enhanced psychological and social functioning (6) Parmenter relates to the duration of replacement treatment. Other study findings also demonstrate the need for continuous protection and provide justification for a strategy adapted to the patient's specific needs and circumstances (13).

Research on the quality of life of addicts is unusual in our country. Thus, the focus of professional attention has changed from clinical efficacy to meaningful care for addicts and the addict community. The objective of the study on the viewpoint and quality of life of opiate addicts was to demonstrate the existence of treatment-related discrepancies between different groups of addicts and to examine the processes behind these differences.

This study seeks to determine if demographic, socioeconomic, and health parameters of respondents, as well as their environment, addiction, and treatment characteristics, have a predictive influence on the quality of life of opiate addicts.

Method

The research was done as an epidemiological cross-sectional study (cross-sectional study) with 70 respondents divided into two groups. The units of observation were opiate addicts with diverse (demographic, socioeconomic, and health) features who were treated at the Clinic for Mental Health Protection of the University Clinical Center in Niš and selected at random.

The research included two groups: the first group consisted of 35 opiate-dependent patients receiving methadone treatment, while the second group consisted of 35 opiate addicts treated with buprenorphine. When selecting participants for the second group, the matching method was used to ensure that all groups of addicts had comparable demographic characteristics, thereby removing the chance of confounding impacts.

The study's power was assessed using data from the scientific literature about the relationship between quality of life and length of methadone treatment. Utilizing the G Power programme and the study's power settings for medium impact strength, data on the 70 required participants were gathered in order to uncover the quality of life indicators with less impact using this approach.

The collection of data in 2020 was undertaken in accordance with the Helsinki Declaration and with the agreement of the Ethics Committee of the Faculty of Medicine in Kragujevac.

An eye-related demographic questionnaire was used to collect data on the respondents' characteristics.

Cross face-to-face interviews with respondents in a health facility to collect data on demographic, socio-economic and health characteristics (gender, age, level of education, employment, marital status, children, number and type of illness), environmental characteristics (housing conditions, living conditions,

characteristics of the family and family functioning, number of friends and relationships with friends), and characteristics of health care (presence of a choose-a-path questionnaire, type of health insurance coverage, and type of health insurance coverage).

The WHO Health Status Questionnaire (WHO EQ-5D, Version 4.0, 2011) was used to collect data on health status (health-related quality of life). A descriptive system (EQ-5D- 5L) that focuses on five dimensions of health (mobility, self-protection, usual activities, presence of pain/discomfort, and anxiety and/or depression) and a visual analogue scale (EQ-5D-VAS) on which the respondent rates his or her health from the worst possible level (0) to the best possible level (100) were utilised in this study (29). Euro QoL was evaluated using the gathered Index EQ-5D data, a quantitative evaluation of healthcare treatment outcomes and an aggregate measure of health and quality of life (30).

The ASI questionnaire (Addiction Severity Index, McLellan, 1992) was used to document the severity of the impacts of addiction in seven domains (health, professional, social, family, legal, addictive, and mental) functioning in the last 30 days and during the respondent's whole life (31). Based on the collected data, the following scores were calculated: Employment Composite Score (ECS), Medical Composite Score (MCS), Psychiatric Composite Score (PCS), Alcohol Composite Score (ACS), Drug Composite Score (DCS), Legal Composite Score (LCS), Family Composite Score (FCS), and Legal Composite Score (LCS) (ECS).

The overall quality of life is represented by the total of the individual's perceived quality of life and the degree of quality of life measured in four unique categories, according to the results of this research (physical functioning, psychological functioning, social functioning, environment).

To generate the WHOQOL – BREF index (32), which analyses the overall quality of life based on the judgments of respondents whoinput their own standards, norms, and expectations, a standardized questionnaire was used to collect data on quality of life. The index provides the respondent's evaluation of his condition, functionality, and contentment with 26 aspects of life on a five-point Likert scale.

Statistical data processing

The frequency distribution of responses by the perception of quality of life category for the two examined groups gives a graphical depiction of quality of life. Using a t-test, it was determined whether or not the differences were statistically significant. Multiple linear regression and correlation were used to investigate and assess prospective factors of relevance for the perceptions and levels of quality of life among addicts. The null hypothesis was performed at $p < 0.05$. Statistical analysis was done in SPSS 16.0.

Results

When compared to addicts who were treated with other methods, those who participated in methadone maintenance programs reported a much worse quality of life view. The differences between the two groups were highly statistically significant ($\chi^2 = 29.86$ DF = 8 $p = 0.000$).

The values of the level of quality of life in the physical health and environment domains were assessed to be somewhat higher among addicts who were participating in the methadone program as compared to addicts who were not participating in the program. Higher quality of life values were assessed in the areas of psychological health and social connections among addicts who were not enrolled in the methadone program. The disparities in quality of life between the different groups investigated did not show statistical significance in any field (Table 1).

Table 1. Life quality descriptive statistical parameters

CATEGORY	DESCRIPTIVE STATISTICAL PARAMETERS						
	X	SD	Cv (%)	Med	SE	Min	Max
Domain: Physical health							
Group A	34.52	3.57	15.05	24	0.63	16	32
Group B	34.48	3.35	15.14	22	0.593	15	29
Domain: Mental health							
Group A	18.78	4.35	23.16	19	0.768	10	27
Group B	20.53	4.41	21.48	20.5	0.780	10	30
Domain: Social relations							
Group A	9.40	2.82	30.00	9.5	0.497	4	15
Group B	10.22	2.35	22.99	10	0.416	6	15
Domain: Environment							
Group A	28.03	4.77	17.02	27.5 0	0.843	17	38
Group B	27.44	4.75	17.31	27.00	0.839	21	39

The analysis of predictors for the perception of quality of life determined the predictive significance of demographic (gender), socio-economic (level of education, type of settlement), and health characteristics of respondents such as functional status (mobility, ability to care for themselves, ability to perform daily tasks), presence of symptoms (irritability/depression), and perception of health, as well as household characteristics (number of household members, number of children). MCS, DCS, LCS, FCS, and PCS can be considered as predictors of quality of life, except for self-care (p = 0.055) (Table 2).

The analysis of predictors for quality of life in the domain of physical health determined the predictive significance of demographic (gender), socio-economic (level of education, marital status, type of occupation, monthly income, type of settlement) and health characteristics of the respondents such as the functional status (ability to perform daily tasks), perception of health, and characteristics of health care, primarily continuity (non-interrupted care) (area of living space per household member, method of heating the living space). In the realm of physical health, determinants of quality of life included features of addiction (ASI indices that describe specific effects related to the type of psychoactive substance used—ACS, DCS, as well as drug addiction experience—how long they took the drug). In terms of an individual's physical health and quality of life, the treatment parameters revealed predictive potential (Table 3). The analysis of predictors for quality of life in the domain of mental health determined the predictive significance of demographic (gender), socio-economic (level of education, type of occupation, monthly income, type of settlement in which he lives), health characteristics such as the functional status of the respondent (mobility, ability self-care), presence of symptoms (pain/discomfort, irritability/depression), relationship, perception of health, health care, above all continuity (number of visits to the general practitioner), as well as household characteristics (number of household members, building where they live, area of living space per household member, method of heating the living space).

According to the findings of the study, the features of addiction were classed as predictors of quality of life in the field of mental health (ASI indices that describe the various effects and consequences of addiction, apart from the effects on employment—MCS, ACS, DCS, LCS, FCS, PCS, as well as the length of drug addiction experience—number of years on drugs) (Table 4).

The duration and frequency of methadone treatment interruptions as the aspects of addiction treatment exhibited a predictive influence on quality of life in the area of mental health.

Table 2. Model of multiple linear regression for the sense of life quality

INDEPENDENT VARIABLES	B	SE	Beta	T-test	P
Medical composite score	-3.789	1.114	-0.884	-2.442	0.033
Comrade composite score	-11.321	3.441	-0.799	-2.113	0.044
Legal composite score	-12.889	3.322	-2.599	-3.431	0.022
Family composite score	11.543	3.665	1.411	3.932	0.011
Psychiatric composite score	-9.663	2.677	-2.299	-3.612	0.022
Mobility	-3.998	1.921	-1.587	-2.432	0.044
Self-care _	-10.112	2.354	-2.599	-3.234	0.055
Everyday activities	-2.012	0.588	-0.444	-2.765	0.044
Irritability/depression	3.002	0.599	1.555	3.432	0.022
Health condition scale	-0.032	0.0440	-1.552	-3.667	0.032
Number of months spent in methadone treatment	0.103	0.023	2.977	4.458	0.007
Number of household members	2.164	0.704	4.245	3.978	0.011
The type of settlement in which they live	2.915	1.019	0.981	2.860	0.035
Number of children	-0.774	0.296	-0.808	-2.619	0.047
Education	1.529	0.480	1.403	3.187	0.024
Gender	-4.175	0.939	-1.753	-4.448	0.007
A constant	10.611	2.831		3.748	0.013

Table 3. Multiple linear regression model for quality of life in the domain of physical health

INDEPENDENT VARIABLES	B	SE	Beta	T-test	P
Alcohol composite score	-176.021	2.993	-1.300	-49.367	0.011
Comrade composite score	21.022	1488	0.398	11.992	0.040
Everyday activities	-7.991	0.209	-0.641	-48.054	0.023
Health condition scale	0.113	0.007	1.033	21.301	0.038
The main reason for visiting a doctor (general medicine. occupational medicine)	3.038	0.122	1.091	24.824	0.026
Number of visits to the general practitioner	0.818	0.034	0.948	24.030	0.026
Living space heating	1.659	0.109	0.625	15.197	0.042
Area of the living space (m^2)	-0.112	0.009	-0.703	-13.168	0.048
The type of settlement in which they live	-5.345	0.387	-0.444	-13.794	0.046
How long have they been taking drugs? Number of years on drugs	-0.539	0.019	-0.724	-28.189	0.023
Type of occupation	-2.539	0.071	-1.061	-35.968	0.018
Monthly income	2.655	0.119	0.990	22.255	0.029
Marital status	1.665	0.073	0.784	22.907	0.028
Education	4.678	0.135	1.053	34.759	0.018
Gender	-10.943	0.270	-1.031	-43.095	0.015
A constant	-10.836	1.440		-7.526	0.048

Table 4. The development of a multiple linear regression model for evaluating quality of life

INDEPENDENT VARIABLES	B	SE	Beta	T-test	P
Medical composite score	-21.022	0.887	-1.443	-21.998	0.022
Alcohol composite score	-160.720	3.991	-1.112	-33.332	0.044
Comrade composite score	-61.002	3.221	-0.998	-23.223	0.033
Legal composite score	-84.991	2.334	-3.223	-35.665	0.022
Family composite score	81.023	2.997	1.665	28.776	0.033
Psychiatric composite score	-50.998	1.777	-2.332	-29.001	0.044
Mobility	-38.184	1.120	-2.565	-34.082	0.019
Self-care	-70.290	1.447	-3.028	-37.531	0.017
Pain/discomfort	-7.577	0.250	-0.871	-30.312	0.021
Irritability/depression	12.027	0.376	1.709	32.028	0.020
Health condition scale	-0.184	0.014	-0.795	-13.099	0.049
Methadone maintenance treatment interruption	-3.284	0.128	-0.755	-25.623	0.025
Number of months spent in methadone treatment	0.451	0.015	2.310	29.325	0.022
Number of visits to the general practitioner	0.692	0.053	0.649	13.047	0.049
Number of household members	12.608	0.357	4.896	35.330	0.018
Living space heating	2.791	0.170	0.850	16.402	0.039
Area of the living space (m^2)	0.250	0.013	0.976	18.794	0.034
The living facility	4.914	0.234	1.109	20.986	0.030
The type of settlement in which they live	14.031	0.604	0.942	23.230	0.027
How long have they been taking drugs? Number of years on drugs	0.463	0.030	0.503	15.537	0.041

Type of occupation	-2.410	0.110	-0.815	-21.898	0.029
Monthly income	2.396	0.186	0.723	12.884	0.049
Education	6.965	0.210	1.269	33.197	0.019
Gender	-17.504	0.396	-1.334	-44.224	0.014
A constant	39.681	2.244		17.680	0.036

Using an analysis of predictors for quality of life in the domain of social relations, the predictive significance of functional status (the capacity to care for oneself) and environmental characteristics was determined. This domain is concerned with the quality of one's interpersonal interactions (number of household members). The predictive value of other variables (demographic, socio-economic, and health factors of the responder, as well as health care characteristics) was not demonstrated. The investigation included the repercussions of addiction as one of the determinants of life quality in the area of social health (ASI indices that describe specific effects, such as ACS, DCS, LCS, FCS).

The treatment features showed no prognostic influence on social relations-related quality of life (Table 5).

The analysis of predictors for the quality of life in the domain of the environment established the predictive significance of the characteristics of the respondent's socio-economic position (marriage status, type of settlement in which he resides), the characteristics describing the respondent's health care, most notably continuity (number of visits to the general practitioner, main reason for the visit), as well as the characteristics of the household (owning and using a car, number of children in the household, and number of pets). All variables included in multivariate model (Table 6) did not have a significant predictive influence on the circulatory domain of quality of life.

Table 5. Multiple linear regression model for social connection domain and quality of life

INDEPENDENT VARIABLES	B	SE	Beta	T-test	P
Alcohol composite score	-82.334	28.223	- 0.765	-3.998	0.111_
Legal composite score	-26.344	15.323	-1.322	-1.132	0.212_
Family composite score	18.556	16.667	0.404	1.987	0.321_
Self-care	-21.887	9.898	-1.221	-2.223	0.123
Number of household members	4.554	3.999	2.565	1.876	0.113_
A constant	-6.232	12.011		-0. 232	0.332 _

Table 6. Model of multiple linear regression for the circulatory domain of quality of life

INDEPENDENT VARIABLES	B	SE	Beta	T-test	P
Employment composite score	4.991	7.778	0.111	0.499	0.666
Alcohol composite score	7.889	70.665	0.032	0.221	0.779
Comrade composite score	-18.798	35.332	-0.443	- 0.443	0.431
Legal composite score	-50.993	35.221	-1.999	-1.221	0.456
Family composite score	19.1889	38.112	0.221	0.332	0.688
Psychiatric composite score	-24.991	25.334	-1.321	-0. 887	0.113
Methadone maintenance treatment interruption	-4.192	1.898	- 0.892 _	-2.208	0.271
Number of visits to the general practitioner	1.663	0.786 _	1.443	2.116	0.281
Availability of access to computers and the Internet	-4.077	2.342	- 0.772 _	-1.740	0.332
The type of settlement in which they live	14.570	8.947	0.905 _	1.628	0.351
How long have they been taking drugs? Number of years on drugs	0.648 _	0.442 _	0.651 _	1.466	0.381
Marital status	-3.705	1.678	-1.306	-2.208	0.271
A constant	30.469	33.246		0.916 _	0.528

Discussion

Although there are no factual differences in any area of quality of life between methadone maintenance programme users and those treated with buprenorphine, the perception is that methadone addicts have a far worse quality of life. Despite the need for more research, it seems that the causes of dissatisfaction are psychological and social in origin.

In terms of purchasing power and quality of life, respondents with a lower score of physical and mental consequences, drug-related consequences, and legal troubles (lower MCS, PCS, DCS, LCS) perceive better scores, regardless of the family implications (higher FCS). These results are similar with the findings of other research (3, 4, 27) on the influence of various addiction-related outcomes on life quality, regardless of whether this impact occurs in conjunction with other respondent characteristics (4) or independently of them (3). Those with fewer difficulties in terms of mobility, ability to care for oneself, and completion of daily duties, and in whom irritability and depression occur less often, report a greater quality of life while ranking their own health less highly. This supports the findings of De Maeyer (8) and Tracy (9) about the connection between health and quality of life (9, 27). Those who have engaged in the methadone maintenance treatment for a longer duration have a higher life quality. This corroborates the results of the vast majority of investigations that reached the same conclusion (5–8, 10, 14–28). In this survey, city-dwelling respondents with a larger family size and fewer children, a higher education level, and a male gender rated the quality of life as better. The results of this study supported those of prior research on the effect of the environment—the household (4, 8, 9), children (1, 2), and social networks (4, 9, 10).

According to the claims of other authors, those with a lower ACS, a higher DCS, and a shorter history of drug dependency should have a better physical health-related quality of life (9, 8). There is a correlation between the reported findings regarding the determining influence of symptoms and chronic problems on physical domain quality of life (12, 9, 8) and the established significance of less frequent difficulties in performing daily activities, higher health ratings, more frequent doctor visits, and more regular control. The outcomes of this research also show the significance of living situations (8, 5, 9). Addicts who dwell in smaller apartments, are heated by steam heating, reside in smaller locations, have non-sedentary employment, better salaries, are married or cohabiting, and belong to groups with a higher degree of education have a superior physical quality of life. Living circumstances give the gender-specific environment (1–3), which may assist to explain the predictive significance of gender, i.e., the superior quality of life experienced by male addicts.

In the domain of mental health, the level of life quality is determined by a relatively different collection of qualities. The length of drug dependency and the severity of its ramifications, as well as the urban setting, have a considerable predictive impact. Subjects with fewer addiction-related consequences should have a superior quality of life in this area (lower MCS, ACS, DCS, LCS, PCS, even when FCS is higher). Psychological quality of life is higher for addicts who have less issues with mobility and self-care, who suffer less pain and discomfort, and who have a more positive self-perception of their health. Respondents with a longer history of drug addiction, who have been in the methadone programme for a longer period of time, who have left the programme less often, and who act protectively in other ways have a higher quality of life in terms of mental health (they turn to a doctor for help more often). Numerous studies have shown that this result is supported by the contribution of the duration and relevance of continued methadone therapy (18, 19). A higher quality of life in the psychological domain is also determined by numerous features of the urban socioeconomic position (higher level of education, higher income, employment, residing in the city, living in bigger conventionally heated residences, a larger number of household members) and by gender (male). From a gender perspective, the predictive function of gender is explicable. Our results reflect the findings of De Maeyer (13) about the impact of drugs, which is realised in combination with other (personal and environmental) factors (life situation, financial situation, changes, perspective, participation in free and social activities, environmental support).

It has also been shown that alcoholism and family support are important determinants of quality of life in the social realm (1, 2, 4, 8, 9, 10, 32). Individuals with lower ACS and LCS, a greater FCS, fewer self-care difficulties, and larger households are more likely to have better social health and quality of life.

It is anticipated that respondents with lower DCS, LCS, and PCS, and higher ECS, ACS, and FCS, who have a longer history of drug addiction, who interrupt their participation in the methadone programme less frequently, who normally seek help from a doctor, who do not have access to a computer, who reside in urban areas, and who are married or in an extramarital relationship, will have a higher quality of life in the domain of environment. Moreover, these findings validate the prior assertions.

Conclusion

The psychological quality of life is higher for addicts who have fewer issues with mobility and self-care, who suffer less pain and discomfort, and who have a more positive self-perception of their health. Respondents with a longer history of drug addiction, who have been in the methadone programme for a longer duration, who have left

the programme less often, and who exhibit other protective behaviors had a greater mental health quality of life (they turn to a doctor for help more often).

Variations in the perception and degree of quality of life across several variables cannot be accounted for by a single predictor. There are several determining elements, and their effect is complex.

Health characteristics, socioeconomic position characteristics of respondents, and other addiction-related outcomes are the most prominent drivers of the degree of quality of life. The relationship between treatment and the level of life quality exists, but it is not obvious.

Participation in the methadone programme affects the addict's outlook and psychological and environmental quality of life. The duration and frequency of methadone treatment interruptions were the most predictive of all treatment characteristics. The impact of methadone treatment characteristics on physical and social quality of life is negligible.

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FAKTORI KOJI DEFINIŠU KVALITET ŽIVOTA U POPULACIJI ZAVISNIKA OD OPIJATA

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Samo razumevanje faktora koji utiču na kvalitet života zavisnika od opijata može poboljšati i kvalitet terapije i njenu efikasnost. Postoji povezanost između načina lečenja i organizacije kompletne zdravstvene službe, što rezultira promenljivim kvalitetom života ovih bolesnika. Osim karakteristika same bolesti zavisnosti, na kvalitet života zavisnika mogu uticati i drugi aspekti života, kao što su demografija, socio-ekonomski status i zdravlje samog zavisnika. Svrha ovog istraživanja bila je da se utvrdi da li određene karakteristike zavisnika, sama bolest zavisnosti i način lečenja imaju prediktivni uticaj na kvalitet života opijatskih zavisnika koji su lečeni korišćenjem dvaju najčešćih pristupa.

Epidemiološko istraživanje studija preseka urađeno je 2020. godine na slučajnom uzorku od 70 opijatskih zavisnika lečenih u Univerzitetskom kliničkom centru Niš (35 zavisnika u programu održavanja metadonom i 35 zavisnika lečenih buprenorfinom). Koristeći standardizovane instrumente za merenje zdravstvenog statusa (engl. *World Health Organization instruments for measuring health status* – WHO EQ-5D), težine posledica zavisnosti (engl. *Addiction Severity Index*–ASI) i kvaliteta života (engl. *standardized World Health Organization quality of life* – WHOQOL), neophodne podatke prikupili smo preko intervjua „licem u lice" sa ispitanicima i to na osnovu nezavisno razvijenog upitnika na osnovu kojeg su izračunati indeksi zdravlja (EQ-5D Index), težina posledica zavisnosti i kvaliteta života (WHOQOL) (WHOQOL-BREF Index). Podaci su kategorisani uz pomoć odgovarajućih tehnika deskriptivne statistike, a grupne razlike procenjene su korišćenjem χ^2 (Hi-kvadrat) testa i T-testa. Koristeći višestruku regresiju i korelaciju, izdvojili smo prediktore.

U pogledu vrednosti indeksa kvaliteta života, ne postoji značajna razlika između zavisnika koji se leče metadonom i zavisnika koji se ne leče metadonom. S druge strane, zavisnici koji se leče metadonom navode da imaju mnogo lošiji kvalitet života od zavisnika koji se ne leče metadonom. Zdravstvene navike, karakteristike socio-ekonomskog položaja ispitanika i drugi ishodi vezani za zavisnost najistaknutiji su faktori sa značajnim stepenom uticaja na kvalitet života. Efekti lečenja postaju sve manje primetni. Metadonski tretman ima prediktivni uticaj na zavisnikov pogled na život, kao i na stepen zadovoljstva (svojim psihičkim zdravljem odnosno okolinom) zavisnika. Trajanje metadonske terapije i bilo kakav prekid u nezi zavisnika dva su najvažnija indikatora. Posledice metadonske terapije, kako na sam organizam, tako i na društvo, sveukupno su blage.

Nemoguće je da se jedan prediktor računa i kao stepen i kao percepcija kvaliteta života u nizu različitih karakteristika. Broj razmotrenih aspekata prilično je velik, a implikacije koje iz toga proizilaze su složene.

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***Ključne reči**: zavisnici od opijata, lečenje, kvalitet života, prediktori*

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SOURCES OF STRESS AMONG UNIVERSITY STUDENTS AND COPING METHODS

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The current literature confirms high-stress exposure in university students. That is why the aim of this study was to identify university students' self-reported sources of stress, and the most common stress coping methods. A cross-sectional study was performed to collect data on the most frequent sources of stress among university students and coping methods. The study included 309 students of the Faculty of Medicine in Foča (Bosnia and Herzegovina), 118 males and 191 females. The students rated the intensity of certain stressful situations on a scale of 1 to 10 and ranked them on an individual stress scale. The highest-ranked sources of stress were defined, and mostly they derived from non-academic sources of stress. The most common stress-coping methods were also defined. The main conclusions were that specific health promotion and stress management programs should be offered to university students in order to cope with strains during their studies.

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Key words: *students, stress, health promotion*

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Introduction

Stress and its impact on students' mental health is an important public health issue. The existing literature confirms the high-stress exposure in medical students. More serious stress events can impair students' mental and physical health, quality of life and life satisfaction, their academic performance and affect their capacity to adequately meet patients' needs in their future medical practice (1). Sources of stress are usually related to education and training, including the examination, entry requirements, teachers and staff behavior toward students and the relationship with staff and clients in different institutions. Non-academic stressors are related to the social environment, family members, relationships with persons who are important to them, and environmental problems (2, 3).

The aim of this study was to determine the most common sources of stress in university students - future medical doctors, as well as stress coping methods they applied in everyday life.

Methods

The study included 309 students of the Faculty of Medicine in Foča, University of East Sarajevo, Republika Srpska (from March to May 2022). There were 191 females (61.8%) and 118 males (38.2%) in the sample.

The original questionnaire was a combination of Youth Stress Scale (YSS-30), i.e. Holmes and Rahe Scale (4), where students rated the intensity of certain stressful situations on a scale of 1 to 10 and ranked them on an individual stress scale, and life events that were cited by students as stressful, and did not adhere to a standard stress scale (4, 5). It also included the demographic characteristics of the surveyed students, and 30 stress events, the most commonly cited in the previous studies, with the possibility for the surveyed students to add three events which represented significant sources of stress for them. Students also answered (in free form) which were their most common stress coping methods (6, 7).

During their lectures, students filled in the above mentioned questionnaire, and it was explained to them what the purpose and importance of the research were. Their participation was voluntary and the anonymity and confidentiality of data was guaranteed. The students' interest in participating in the study was high, so the response rate was 100%. Students

were asked to evaluate each of the potential sources of stress, by their intensity of impacts, on a scale of 1 to 10 and then they ranked them on an individual stress scale. Completing the questionnaire required about 20 minutes.

Statistical analysis was performed using the software package SPSS version 18.0. The main research results are presented in tables and figures. The statistical significance was set at $p < 0.05$. The study procedures were carried out in accordance with the Declaration of Helsinki.

Results

A total of 309 students filled in the questionnaires and all of them completed it in an appropriate way usable for research purposes. The response rate was 100%. In this sample, there were 118 males (38.2%) and 191 females (61.8%).

The ten most frequent sources of stress, as shown in Table 1, were:

Death of a family member, serious illness of a family member, misfortune of the loved one, financial problems, economic crisis, loss of youth (hypothetical), lying and deception by the close ones, unwanted pregnancy, disagreement with parents, big economic loss, and failing the year of study.

The first ranked situations derived from non-academic sources of stress mainly derived from the family, and from contacts with important persons (partners, friends, relatives).

Average values of perceived intensity of all stress events were higher in females than in males ($p < 0.01$). Significant differences were found in the following situations: serious illness of a family member, the misfortune of the loved one, disagreement with parents, separation from family, worry that "I am not able to meet all demands of study and practice", and feeling that "I am not secure enough in my environment".

In the group of academic sources of stress, failing the year of study was ranked as the highest. There were differences in its ranking according to the gender of respondents. The average intensity values of the majority of stress sources were higher in females than in males. Females trusted in their own work efficiency less than males did. The gender differences in the responses are shown in Figure 1.

The most cited stress coping methods that students practiced were "Conversation with friends", and "Support from family members" (Table 2). Different forms of social support, such as stress coping methods, ranked highest. Support from family members was in the 2nd place in the females, and in the 5th place in males (Figure 1, Table 2). Females used crying for stress problems more often than males did. "I'm crying" in females was in the 4th, in males at 14th place in rank ($p < 0.05$). Males most often use intense physical activity ($p < 0.01$) as stress coping method

Table 1. Perceived intensity of stress reactions in the surveyed students

Stressors/Stress event	Total (N = 309)		Males (N = 118)		Females (N = 191)		Comparison M/F*	
	Rating	Intensity	Rating	Intensity	Rating	Intensity	T	p
Death of a family member	1	9.30 ± 2.00	1	8.67 ± 2.87	1	9.43 ± 1.76	1.62	0.105
Serious illness of a family member	2	8.84 ± 1.95	2	8.22 ± 2.10	2	8.97 ± 1.91	2.39	0.017
Misfortune of my loved one	3	8.39 ± 1.72	4	6.78 ± 2.32	3	8.71 ± 1.38	3.83	0.001
Financial problems, economic crisis	4	7.58 ± 2.25	3	7.06 ± 2.51	4	7.68 ± 2.20	0.90	0.368
Losing of youth (hypothetical)	5	7.28 ± 2.75	5	6.56 ± 2.66	6	7.42 ± 2.76	1.39	0.166
Lies and deception by people who are close to me	6	7.27 ± 2.18	7	6.33 ± 2.64	5	7.45 ± 2.05	1.72	0.085
Unwanted pregnancy	7	6.86 ± 3.09	10	6.00 ± 3.28	8	7.02 ± 3.05	1.37	0.171
Disagreement with parents	8	6.81 ± 2.72	15	5.33 ± 2.89	7	7.10 ± 2.61	2.40	0.016
Big economic loss	9	6.67 ± 2.55	11	6.00 ± 2.89	9	6.80 ± 2.48	1.18	0.240
Failing the year of study	10	6.64 ± 2.89	6	6.56 ± 2.48	13	6.66 ± 2.98	0.44	0.661
Permanent loss of a friend	11	6.63 ± 2.47	12	6.00 ± 2.57	10	6.76 ± 2.44	1.29	0.198

Partner's infidelity	12	6.60 ± 2.97	8	6.28 ± 2.56	12	6.67 ± 3.05	0.89	0.372
Separation from family	13	6.35 ± 2.96	22	4.33 ± 3.14	11	6.75 ± 2.77	2.89	0.004
Separation from a loved one	14	6.27 ± 2.50	13	5.78 ± 2.10	14	6.36 ± 2.57	1.23	0.218
Limited time for recreation and social activities	15	6.05 ± 2.69	14	5.61 ± 2.99	17	6.13 ± 2.63	0.79	0.427
Exams	16	5.97 ± 2.52	17	5.00 ± 2.7	16	6.16 ± 2.45	1.63	0.104
Worry that I am not able to meet all the demands of study and practice	17	5.86 ± 2.49	23	4.33 ± 2.59	15	6.17 ± 2.37	2.82	0.005
Feeling that I am not secure enough in my environment	18	5.69 ± 3.03	28	3.78 ± 2.60	18	6.08 ± 2.97	2.93	0.003
Excessive workload	19	5.61 ± 2.48	26	3.83 ± 2.31	19	5.97 ± 2.37	3.23	0.001
Organization of study and practical work by faculty	20	5.61 ± 2.79	16	5.11 ± 3.22	22	5.70 ± 2.70	0.86	0.391
Inadequate communication and support by staff	21	5.60 ± 2.51	24	4.28 ± 2.72	20	5.86 ± 2.40	2.48	0.013
Administrative jobs at the faculty	22	5.60 ± 3.02	9	6.22 ± 2.78	26	5.47 ± 3.06	0.96	0.339
Request for perfect performance in work with clients	23	5.56 ± 2.40	20	4.50 ± 2.71	21	5.78 ± 2.29	2.13	0.034
Unsupportive environment during practical work	24	5.39 ± 2.40	18	4.72 ± 2.59	25	5.52 ± 2.35	1.33	0.184
Literature availability for exam preparation	25	5.39 ± 2.30	19	4.61 ± 2.48	23	5.55 ± 2.24	1.49	0.135
Fight with someone	26	5.28 ± 2.76	21	4.44 ± 2.66	27	5.44 ± 2.77	1.35	0.177
Belief in own work efficiency	27	5.17 ± 2.64	29	3.33 ± 2.35	24	5.54 ± 2.54	3.18	0.001
Teachers and staff behavior toward students	28	4.82 ± 2.45	27	3.83 ± 2.68	28	5.01 ± 2.37	2.09	0.037
Being overweight	29	4.06 ± 2.96	30	3.28 ± 2.61	29	4.22 ± 3.01	1.19	0.235
Watching the game when my favorite team loses	30	3.60 ± 2.96	25	3.94 ± 3.19	30	3.53 ± 2.93	0.76	0.447
Total		6.23 ± 2.58		5.36 ± 2.67		6.40 ± 2.52	2.93	0.003

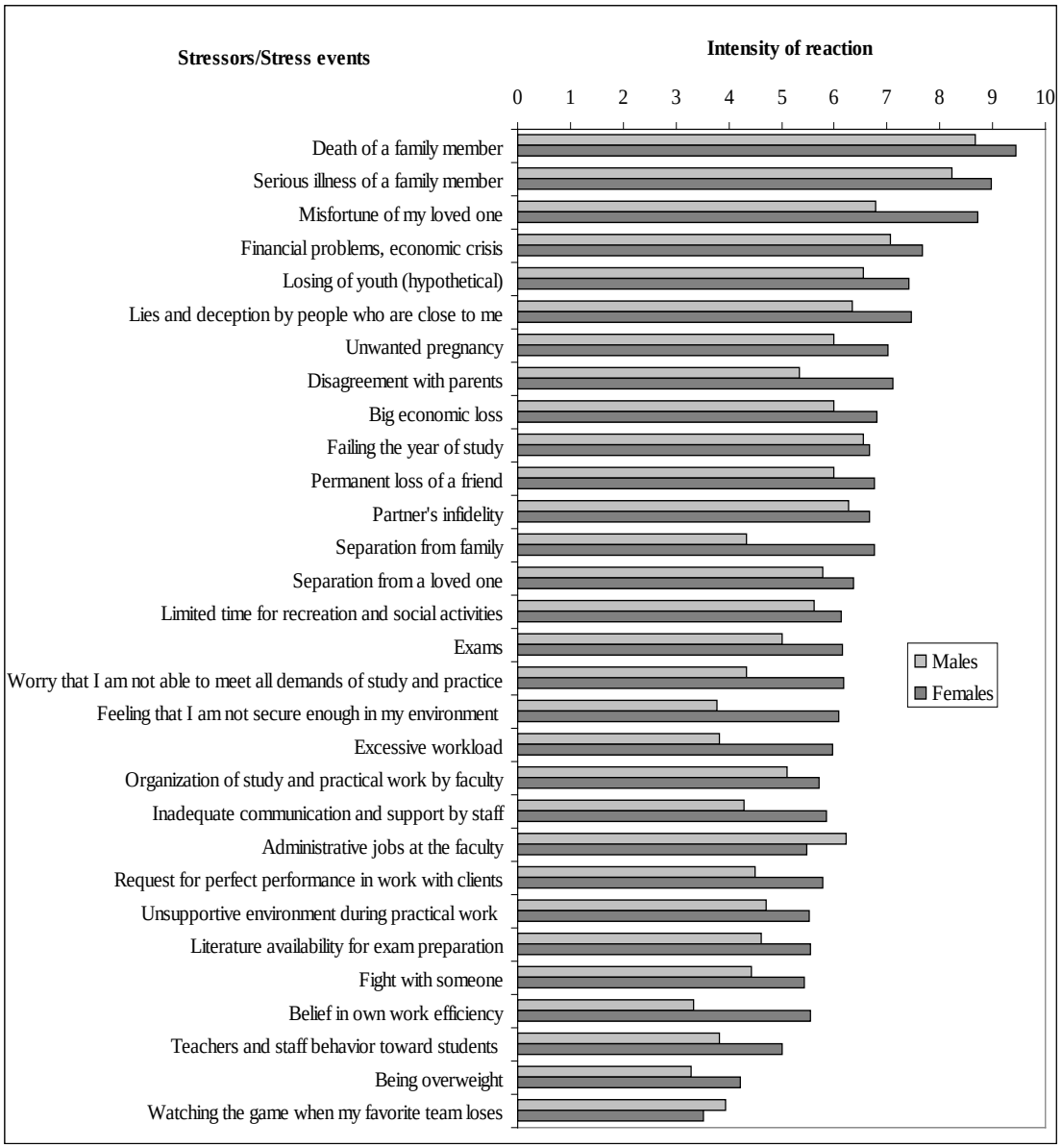

Figure 1. Stress events and perceived intensity of stress reaction in students, both genders

Table 2. Stress coping methods of the surveyed students

Methods	Males+Females (N = 309)		Males (N = 118)		Females (N = 191)		Comparison M/F*	
	Rating	Number	Rating	Number	Rating	Number	Chi square	*p*
Conversation with friends	1	88 (80.7%)	1	13 (72.2%)	1	75 (82.4%)	1.00	0.316
Support from family members	2	77 (70.6%)	5	9 (50.0%)	2	68 (74.7%)	4.43	0.035
Listening to music	3	74 (67.9%)	4	10 (55.6%)	3	64 (70.3%)	1.50	0.220
Socializing and going out	4	56 (51.4%)	2	11 (61.1%)	6	45 (49.5%)	0.82	0.366
Walks	5	55 (50.5%)	6	9 (50.0%)	5	46 (50.5%)	0.01	0.966
“I'm crying”	6	52 (47.7%)	14	3 (16.7%)	4	49 (53.8%)	8.33	0.004
“I'm sleeping”	7	40 (36.7%)	11	4 (22.2%)	7	36 (39.6%)	1.94	0.163
Prayer	8	36 (33.0%)	12	4 (22.2%)	8	32 (35.2%)	1.40	0.494
Reading books, magazines	9	34 (31.2%)	9	5 (27.8%)	9	29 (31.9%)	0.12	0.732
Internet	10	32 (29.4%)	10	5 (27.8%)	10	27 (29.7%)	0.03	0.872
Intense physical activity	11	31 (28.4%)	3	11 (61.1%)	13	20 (22.0%)	11.31	0.001
Relaxation	12	30 (27.5%)	7	9 (50.0%)	12	21 (23.1%)	5.46	0.019
TV	13	30 (27.5%)	8	6 (33.3%)	11	24 (26.4%)	0.36	0.546
I shout and argue	14	22 (20.2%)	15	3 (16.7%)	14	19 (20.9%)	0.38	0.825
Alcohol	15	21 (19.3%)	13	4 (22.2%)	15	17 (18.7%)	0.12	0.728
Cigarettes	16	15 (13.8%)	18	1 (5.6%)	16	14 (15.4%)	1.22	0.269
Sedatives	17	7 (6.4%)	16	3 (16.7%)	17	4 (4.4%)	3.76	0.052
Drugs	18	3 (2.8%)	17	2 (11.1%)	19	1 (1.1%)	5.63	0.018
Professional help	19	3 (2.8%)	19	1 (5.6%)	18	2 (2.2%)	0.82	0.663

*Pearson Chi-square test

Discussion

Stress events ranked most highly where stemmed by good relationships with family members, partners, friends and social environment. Misfortune of the loved one, financial problems, economic crisis, loss of youth, lies and deception by the close ones, unwanted pregnancy, disagreement with parents and big economic loss did not have any statistical importance. The sources of stress were largely derived from family and social environment, or associated with socioeconomic factors. The surveyed students have chosen to be medical doctors, and that could be a reason why they were more focused on individual, family and social environment, and therefore reacted more intensely to the sources of stress derived from these issues. They have lived in a country with socioeconomic transition and instability for almost 30 years, and in these situations, especially according to Maslow's hierarchy of needs, the motivation for survival (personal or family) is increased, and incentives for self-actualization through academic training are reduced (8–10).

In the present study, female gender was a significant predictor of higher intensity of reaction to stress. Significant differences depending on the gender of the respondents were found in the following situations: serious illness of a family

member, misfortune of the loved one, disagreement with parents, and separation from family (as it was found in other similar studies). Worry that “I am not able to meet all demands of study and practice“, excessive workload, inadequate communication and support by staff, request for perfect performance in work with patients, belief in own work efficiency, and teachers and staff behavior toward students were also emphasized (11). Females considered themselves to be less effective at work than males and, were able to express their feelings more easily (e.g. crying), including those associated with stressful situations. In the literature review on gender differences in terms of self-confidence, it is described that females had lower levels of self-confidence, which could also be one of the reasons why their stress responses were more intense than in male students (12).

Students used various stress coping methods. Support from friends and family members has proven to be very important in stressful situations (ranked in 1st and 2nd place of coping methods), and therefore stressful events related to the family, partners and friends were a significant source of stress for our students. Maslow's revised pyramid of needs also gives the highest priority to partnership and parenting (13, 14).

Different forms of "self-help" methods were used, like venting stress through crying (typical for females), or intense physical activity, relaxation, socializing and going out (more typical for males), listening to music, prayer, reading books, magazines, internet, TV, alcohol, cigarettes, sedatives and drugs. Similar results were found in available literature (15, 16). Seeking professional help was on the last place in the rank, and that form of help should be organized by their universities (17, 18).

The contribution of the study is that certain non-academic sources of stress were defined by future medical doctors as highly significant stressors. Derived student's scale of stress contained many stress events which are not presented on the standard adult's stress scales. Statistically significant gender differences were found in the perception of certain stress events, as well as differences in the ranking of stress events by female and male students. Coping strategies used by them are wide-ranging and mostly were not appropriate (19, 20).

Conclusion

Specific courses of mentoring programs and stress management should be offered in order to cope with strains during the study of university students. In addition, gender-specific access to programs for cognitive-behavioral stress management should be based on those findings.

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IZVORI STRESA MEĐU STUDENTIMA I METODE SUOČAVANJA SA STRESOM

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Dosadašnja literatura potvrđuje visoku izloženost stresu kod studenata. Zbog toga, cilj ove studije bio je da se identifikuju izvori stresa koje su studenti sami prijavili, kao i najčešće metode suočavanja sa stresom. Urađena je studija preseka kako bi se prikupili podaci o najčešćim izvorima stresa među studentima i o metodama suočavanja sa stresom. Istraživanjem je obuhvaćeno 309 studenata (118 studenata muškog pola i 191 student ženskog pola) Medicinskog fakulteta u Foči, u Bosni i Hercegovini. Studenti su ocenjivali intenzitet pojedinih stresnih situacija na skali od jedan do deset i rangirali su ih na individualnoj skali stresa. Definisani su najviše rangirani izvori stresa, i to uglavnom iz neakademskih izvora stresa. Takođe, definisane su najčešće metode suočavanja sa stresom. Došlo se do zaključka da studentima treba ponuditi specifične programe promocije zdravlja i upravljanja stresom kako bi se nosili sa naporima tokom studija.

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LOSS OF INTERSTITIAL CELLS OF CAJAL IN THE SMALL INTESTINE OF RATS WITH DIABETES MELLITUS

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Diabetic gastroenteropathy is a common complication in diabetes mellitus. Disturbance of interstitial cells of Cajal (ICC) distribution plays a significant role in the development of intestinal motility dysfunction.

The aim of this study was to investigate the alterations of the intramuscular and myenteric ICC in the small intestine of rats with diabetes mellitus.

Male Wistar rats were used and diabetes was induced by streptozotocin-nicotinamide (STZ-NA) application. The small intestine specimens were exposed to c-Kit antibody to investigate the ICC. Morphological changes of the cells were quantified by the numerical areal density of intramuscular ICC, and the ICC score of myenteric ICC. Results showed loss of ICC and their network in the small intestine in the diabetic group.

In conclusion, a statistically significant decrease in the number of intramuscular ICC and myenteric ICC was observed in all examined parts of the small intestine in rats with diabetes mellitus. Diabetes mellitus significantly changes the microenvironment of ICC and most likely the reduced signaling by insulin affects ICC and causes their loss.

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Key words: *interstitial cells of Cajal, diabetes mellitus, small intestine, gastroenteropathy*

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Introduction

Diabetes mellitus (DM) is a chronic systemic disorder of glucose metabolism characterized by hyperglycemia. Complications of diabetes include a broad group of disorders resulting from vasculopathy and neuropathy caused by hyperglycemia and oxidative stress. Diabetes affects almost all parts of the gastrointestinal tract (GIT), but the exact prevalence of diabetic gastroenteropathy is unknown, and the main reason for this is that gastroenteropathy symptoms are often attributed to other causes and accompanying diseases (1). There are data in the literature that complications of gastrointestinal motility, such as abdominal discomfort, gastroparesis, nausea and vomiting, diarrhea, slowed intestinal transit and constipation, occur even in 50 – 70% of patients after a ten-year illness (2, 3). Recent studies have shown that neuropathy is not the only cause of enteric gastroenteropathy, but that the loss of interstitial cells of Cajal (ICC) plays a significant role in the development of intestinal motility dysfunction (4). Complex and multifactorial mechanism of diabetic gastroenteropathy includes changes and loss of autonomic nervous system nerve fibers, myenteric plexus glia cells, smooth muscle cells and ICC (5).

A diverse group of intestinal cells in the digestive tract are responsible for the establishment and adequate functioning of intestine motility (6, 7). Based on different patterns of distribution, localization, morphological and functional characteristics, ICC are classified into several subtypes: myenteric ICC (ICC-MY) form a cellular network around the myenteric plexus between the circular and longitudinal muscle layers; intramuscular ICC located within circular (ICC-IMc) and longitudinal (ICC-IML) muscle layer; submucosal (ICC-SM) located at the border between the submucosal connective tissue and the inner muscle layer, septal (ICC-SEP) localized within the connective tissue septa surrounding the muscle bundles (8). The most important cells for maintaining intestinal peristalsis are ICC-MY and ICC-IM cells, which play the role of pacemaker determining the amplitude and frequency of slow waves, inhibitory neuromodulation and act as stress receptors and sensory transductors (9, 10).

Unlike numerous studies related to diabetic gastroparesis (11 – 15), studies that evaluate the

ICC in intestinal dysfunction in diabetes are rare, primarily due to the difficulties of the available methods of diagnosis (muscular wall of the intestine is not involved during routine biopsy of the intestine, and it is also difficult to reach the appropriate anatomical locations endoscopically) (16, 17). The effect of diabetes on the small intestine and colon motility has not been sufficiently studied, although an increased prevalence of constipation and diarrhea has been observed in patients with DM. Initial studies indicated that intestinal transit duration is slowed in animal models of DM, leading to bacterial overgrowth and consequent diarrhea (18), while other studies have shown the presence of accelerated intestinal transit in experimental models (19). This accelerated intestinal transit has been attributed to autonomic neuropathy and DM-induced denervation of sympathetic nerve endings. Prolonged intestinal transit time and constipation are common in patients with DM (1).

The aim of the present study was to identify distribution of intramuscular and myenteric ICC in the small intestine of rats with streptozotocin/ nicotinamide induced diabetes mellitus.

Materials and methods

Animal model

For this study small intestine sections from male Wistar rats (10 weeks old, weighting 230 – 250 g) were used. Experimental protocol used in this study was created in accordance with the National Guide for the Care and Use of Laboratory animals (Serbian Academy of Sciences and Arts, Serbia) and with the Rulebook for handling laboratory animals (Faculty of Medicine, University of Niš, Serbia), and approved by the Ethics Committee of the Faculty of Medicine, University of Niš, Serbia (permit number 12-519/7). Research was performed as a part of the Internal Project no. 38/20 of Medical Faculty of Niš at the Research Center of Biomedicine and Department of Histology and Embryology.

During the experiment, rats randomly divided into control (C) and diabetic (D) groups, were housed in plastic cages, within a controlled environment (constant air ventilation, humidity and temperature of 20 °C ± 2 °C, 12 h light/dark cycle and limitless access to food and water). Diabetes mellitus was induced by the combined usage of intraperitoneal injection of nicotinamide (Sigma Aldrich, USA) at a dose of 110 mg/kg in saline solution and intraperitoneal injection of streptozotocin (Sigma Aldrich, USA) at a dose of 45 mg/kg in ice-cold 0.1 mol/l citrate buffer (pH 4.5) according to the modified model described by Masiello et al. (20). Three and seven days after streptozotocin/nicotinamide (STZ-NA) administration, hyperglycemia was verified in the D group, using glucose meter Accu-check Performa (Roche Diagnostics, USA). In compliance with standard diabetes diagnostic criteria, animals with glucose level above 8.3 mmol/l were considered diabetic, while the animals, with glycemia results below the specified threshold, were excluded from D group. There were 10 animals in each of the C and D groups. At the same time commercially available rat enzyme-linked immunosorbent assay (ELISA) kit using rat insulin as the standard (Mercodia, Upsala, Sweden; catalog number 10-1250-01) was used to measure serum insulin levels. After six weeks from STZ/NA administration, the animals were sacrificed via exsanguinations through the bilateral thoracotomy in deep anesthesia (ketamine hydro-chloride, 100 mg/kg body weight). During the whole experimental period, animal body weight was monitored once a week after the overnight fasting and on the day of sacrifice, along with the daily monitoring of food and water intake.

Tissue preparation

Immediately after the sacrifice, the entire gastrointestinal tract of the animals was dissected in a block via an abdominal incision. Of this, the samples of small intestine (duodenum, jejunum and ileum separately) were specifically removed, treated and washed with saline solution. The obtained samples were fixed in 10% buffered formalin for 24 hours, after which they were paraffin-embedded using standard histological procedure and sequentially sectioned. 4 – 5 μm thick sections were stained using routine Hematoxylin and Eosin (HE) method, and c-Kit immunohistochemistry.

Immunohistochemistry

The slides were deparaffinized (at 58 °C degrees with xylene) and rehydrated in descending series of ethanol (100%, 96%, 70%) and distilled water, after which antigen retrieval solution, 45 minutes at 95 – 98 °C, using the EnVision Flex visualization kit (DM 828, 50x, Dako, Denmark) was applied. After the three rinses in distilled water, 3% hydrogen solution was used for 10 minutes. Primary antibody, Rabbit monoclonal anti-c-Kit (CD117) antibody (Abcam, Cambridge, UK, Ab32363 -dilution 1:100), was incubated overnight at 4 °C. The slides were then treated with secondary antibodies, (EnVisionTM FLEX High pH, code number K8000, Dako, Denmark) for 45 min at the room temperature. The resultant immune complexes were visualized using the Daco REAL EnVisionTM Detection System (Dako, Denmark). The slides were counterstained with hematoxylin, dehydrated in ascending series of alcohols (70%, 96%, 100%), and cleared with xylene.

Qcantitative Image Analysis

All slides were analyzed using an Olympus BX50 light microscope equipped with a Leica DFC

295 digital camera (Leica Micro-System, Reuil-Malmaison, France) with magnification at x200.

The microphotographs for quantitative image analysis were obtained by systematic random sampling method on Olympus BX50 light microscope equipped with a digital camera Leica DFC 295 digital camera (Leica Micro-System, Reuil-Malmaison, France). Numerical areal density analysis (NA) of intramuscular ICC, i.e. average number of cells per mm^2 of the circular and longitudinal muscle layer, was determined using ImageJ software (National Institute of Health, Bethesda, MD, USA; http://imagej.nih.gov/ij/). The cells were counted manually in order to avoid c-Kit positive mast cells which have different characteristics from ICC, like their shape, granular content and localization.

The assessment of myenteric ICC was done by estimating encirclement percentage of the ganglion by the processes of ICC-MY, i.e. ICC score (MP-sore), the semiquantitative method described by Den Braber-Ymker (21).

Analysis of the data obtained using the software SPSS Statistics (version 20, SPSS, Chicago, USA) was performed. The obtained data values were interpreted and compared using the Kruskal-Wallis test with Mann-Whitney U post hoc test.

Results

Establishment of the diabetes mellitus rat model

Glycemia values two hours after feeding in the D group (12.18 ± 0.73 mmol/L) were significantly higher ($p < 0.001$) compared to the control group (6.38 ± 0.61 mmol/L). Further, serum insulin values showed significantly lower values in the D group (192.15 ± 20.17) than in the C group (219.04 ± 18.9). There was no significant difference in body weight ($p > 0.05$) in the D group compared to the control group, however, moderate polydipsia and polyphagia were observed in the D group rats. Glycemia values two and eight hours after feeding, as well as body mass at the end of the experiment are shown in Table 1.

Table 1. Average values of glycemia 2 and 8 hours after a meal, serum insulin values and body weight at the end of the experiment

parameters	group	*N*	*X*	*SD*
2 h glycaemia (mmol/L)	Control	10	6.38	0.61
	D-group	10	12.18	0.73
8 h glycaemia (mmol/L)	Control	10	4.76	0.19
	D-group	10	6.73	0.38
Serum insulin levels (pmol/l)	Control	10	219.04	18.9
	D-group	10	192.15	20.17
Final body weight (g)	Control	10	397.50	11.38
	D-group	10	406.67	20.15

N-number of exp. animal, X-mean, SD-standard deviation

There was no difference in the thickness of the muscle wall between groups and also, no signs of necrosis, apoptosis, or infiltration by neutrophils or lymphocytes observed in all samples of the small intestine of the D group. On the histological sections of the small intestine, four layers were observed, going from the lumen to the surface: mucosa, submucosa, muscular layer consisting of circular and longitudinal sublayer and serosa. On immunohistochemical preparations stained with c-Kit, two types of c-Kit immunoreactive cells were observed, spindle-shaped or stellate multipolar ICC and oval mast cells with a large round nucleus without cytoplasmic appendages (Figure 1).

Distribution of c-Kit immunoreactive ICC subtypes of small intestine in the control and D groups are shown in Figure 1. Intramuscular ICCs of the circular muscle layer, on cross-sections, extended between smooth muscle cells, parallel to their axis. These cells were elongated spindle-shaped, with two long cytoplasmic processes starting from opposite ends of the cell body. On most of the cytoplasmic extensions of c-Kit immunoreactive cells of the circular layer, their branching could be observed, and some of the processes were connected to the corresponding extensions of neighboring cells. These cells were mostly single, scattered throughout the thickness of the circular muscle layer. On the longitudinal sections of the outer muscular layer of the GIT, no secondary branches of the ICC cytoplasmic extensions were observed, nor were their extensions in contact with neighboring cells. These ICC-IM cells were single and sparsely scattered throughout the longitudinal muscle layer.

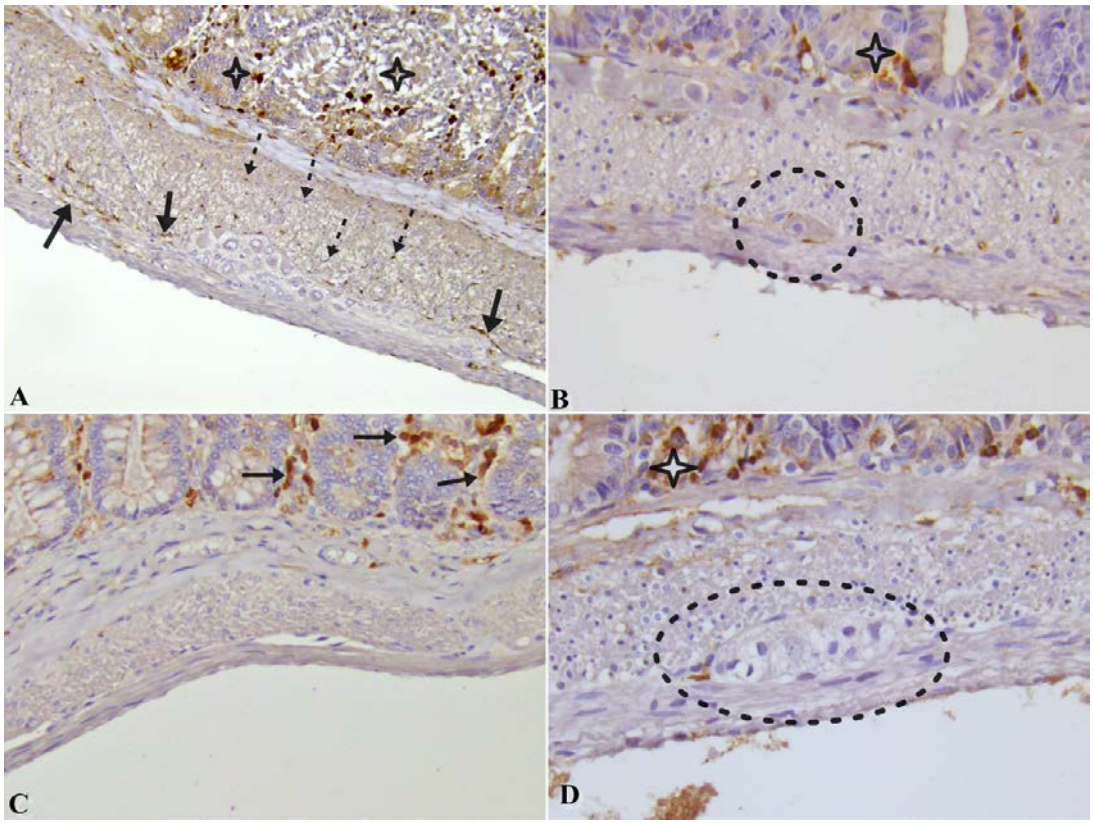

Figure 1. C-Kit immunohistochemistry of the small intestine of control (A, B) and D (C, D) group. A) on the cross-section of the jejunum, c-Kit immunoreactive mast cells are present in large numbers in the mucosa (asterisk); ICC-IM are located between smooth muscle cells, dominantly in the circular muscle sublayer (dashed arrows); ICC-MY are located around the MP ganglion, but do not completely surround it (arrow). B) on the cross-section of the ileum, ICC-MY are located around the MP ganglion (dashed circle); mast cells are present in the submucosa (asterisk). C) cross section of the jejunum; c-Kit immunoreactive mast cells are present in the mucosa and submucosa (arrow); in the smooth muscle layer there are no c-Kit immunoreactive ICC-IM and ICC-MY. G) cross section of the ileum; one c-Kit positive ICC-MY can be seen around the MP ganglion (dashed circle), c-Kit positive mast cells in the mucosa (arrow), c-Kit positive ICC-IM are rare in the muscle layer. A, C x 200; W, D x 400.

In the area of the myenteric plexus, star-shaped, multipolar c-Kit immunoreactive cells, which correspond to ICC-MY, were observed. These cells have long processes that connect and their appendages completely surround the edges of the ganglion of the myenteric plexus (Figure 1B).

Both types of ICC, with the same morphological characteristics as in the control group, were present in the D group. In contrast to the control group, ICC-IM were rare (Figure 1C, D). ICC-MY were also present in the D group, but much less frequently (Figure 1D) and did not completely surround the ganglions of the MP. MP ganglions with no c-Kit immunoreactivity in their surroundings were observed.

The average NAICC and the NA of intramuscular ICC subtypes values in the duodenum, jejunum and ileum of both the D and the control groups are shown in Table 2. The NA values are significantly lower in the D group ($P < 0.001$), compared to the control, as well as the NAICC values of the ileum in relation to the duodenum and jejunum within the control group.

Table 3 shows the average values of the degree of MP ganglion encirclement, i.e., ICC-score of the control and D groups. Testing the average values of ICC-score showed a statistically significantly lower density of MP-score ($P < 0.001$) in the D group compared to the control group in all samples of the small intestine.

Table 2. Numerical areal density (NA) of intramuscular ICC of the circular (ICC-IMc) and longitudinal (ICC-IML) muscle layer of the rat small intestine in the control and D groups

Small intestine region	parameter	group	*N*	*X*	*SD*	*CV*	*Mann-Whitney*
duodenum	N_A ICC	control	105	125.28	28.58	22.81	Z=9.943
		D-group	105	67.04	33.79	50.41	* P=0.000
	N_A ICC-IMc	control	105	106.37	33.82	31.80	Z=11.852
		D-group	105	34.60	18.59	53.71	* P=0.000
	N_A ICC-IML	control	105	10.16	4.50	44.29	Z=6.489
		D-group	105	5.85	3.55	60.66	p=0.000
jejunum	N_A ICC	control	102	120.72	40.03	33.16	Z=5.584
		D-group	102	88.03	37.65	42.78	* P=0.000
	N_A ICC-IMc	control	102	91.21	30.59	33.54	Z=11.296
		D-group	102	27.98	22.46	80.29	* P=0.000
	N_A ICC-IML	control	102	14.13	4.88	34.50	Z=5.978
		D-group	102	9.80	4.79	48.89	* P=0.000
ileum	N_A ICC	control	102	107.54	28.91	26.88	Z=5.793
		D-group	102	78.32	39.23	50.09	* P=0.000
	N_A ICC-IMc	control	102	80.79	21.57	26.70	Z=11.547
		D-group	102	26.00	19.43	74.73	* P=0.000
	N_A ICC-IML	control	102	10.66	5.88	55.10	Z=2.705
		D-group	102	8.63	4.50	52.19	* P=0.007

N – number of analyzed visual fields, X – mean value, SD – standard deviation, CV – coefficient of variation, NA-numerical areal density – the average number of cells per mm2 of the circular and longitudinal muscle layers. * – statistical significance

Table 3. Myenteric interstitial cells of Cajal (ICC-MY) score in the muscle layer of the rat small intestine in control and D group

Small intestine region	group	*N*	*X*	*SD*	*CV*	*Mann-Whitney*
			MP-score (%)			
duodenum	control	109	52.11	16.89	32.41	Z=9.031
	D-group	103	22.72	20.40	89.78	* P=0.000
jejunum	control	103	49.81	13.93	27.97	Z=8.510
	D-group	103	23.50	19.78	84.16	* P=0.000
ileum	control	107	53.36	16.76	31.42	Z=10.702
	D-group	103	18.26	16.76	91.79	* P=0.000

N – total number of evaluated ganglions, X – mean value, SD – standard deviation, CV – coefficient of variation, * – statistical significance

Discussion

The STZ-NA is widely used as an animal model of diabetes that corresponds to diabetes mellitus in humans, and is characterized by mild non-fasting hyperglycemia and slightly decreased insulin levels. Benefits of this animal model are that animals do not require exogenous insulin to survive and live longer so complications of diabetes can be analyzed (22). In addition, this model of diabetes proved to be suitable for examining the morpho-functional changes of ICC in the absence of complications of diabetes such as neuropathy and the effect of nerve fiber loss on ICC by nicotinamide dosage, and experimental duration (23).

Obtained results showed that ICC-IMc density is significantly higher in the circular muscle layer compared to the density of ICC-IML in the longitudinal sublayer in all small intestine regions. This distribution of ICC-IM is similar to the described distribution of ICC in the fetal and adult GIT of humans and rats (8, 24). The fact that smaller regions of tissue provide pacemaker activity for larger sections of circular and longitudinal muscles could explain the differences in the density of circular and longitudinal ICC-IM. Namely, Connor (25) observed in experimental studies that the separation of the circular from the longitudinal muscle layer of the small intestine inactivates the circular muscle, while the isolated longitudinal muscle retains its activity. The authors concluded that slow waves of peristalsis arise in the longitudinal layer and are amplified and propagated through ICC-IM. Also, muscle thickness of circular sublayer is higher than the outer longitudinal one and therefore a higher density of ICC-IM is needed for multiplication and propagation of the electric wave of peristalsis.

Intramuscular ICC of the small intestine are not elongated, spindle-shaped and densely distributed like ICC-IM of the stomach and large intestine (15, 23). In the small intestine, ICC-IM are rarely distributed and it seems that they do not cross-link. These results are consistent with the findings of Horiguchi and Mazet of ICC distribution in the GIT of guinea pigs and dogs (26, 27). Analysis of NA values of intramuscular ICC showed that the number of ICC significantly decreases in the small intestine, from the pylorus to the ileum, compared to the stomach and colon (23). The differences in the number of ICC-IMc of the small and large intestine can be explained by the fact that the smooth muscle cells of the colon, which are not well connected to each other by gap junctions, receive nerve signals through a rich network of ICC-IM, i.e., here ICC help "electrical" communication between smooth muscle cells. In the small intestine, smooth muscle cells of the circular layer are extremely well interconnected by gap junctions, which was shown by Seki and Komuro (28) by analyzing the expression of connexin 43 in the smooth muscle cells of the GIT in the guinea pig. Such mutual connection of smooth muscle cells enables the smooth muscle cells in the small intestine to function as a kind of syncytium, and accordingly, here ICC-IM are less numerous because they do not establish connections with each individual smooth muscle cell. Also, in the small intestine preganglionic vagal neurons innervate smaller groups of certain myenteric neurons, in contrast to the upper parts of the GIT where numerous connections with myenteric neurons are established. The differences in innervation by parasympathetic preganglionic fibers are reflected in the fact that the central nervous system has a much greater direct influence on the upper (esophagus and stomach) and most distal (sigma and rectum) parts of the GIT, and much less directly controls the functions of the small intestine and colon (29, 30).

In the small intestine, the average values of the areal numerical density of ICC-IM are statistically significantly lower in the ileum, compared to the duodenum and jejunum. The assessment of the ICC-score showed that there is no difference within different locations of the small intestine. The results of this study show that the number of intramuscular ICC and myenteric ICC is significantly lower in the group with diabetes. A similar loss of ICC has been observed in the small intestine and colon of experimental animals with diabetes (31, 32). Yamamoto et al., using the db/db model of type 2 DM, showed a reduced number of ICC in the small and large intestine (14).

The mechanism of ICC loss in diabetes has not yet been sufficiently investigated. The causes of the loss of these cells could be due to hyperglycemia and accompanying oxidative stress, reduced insulin levels and the absence of steel factor (stem cell factor), which is secreted by smooth muscle cells from the ICC environment under the influence of insulin and insulin-like growth factor (6, 13). Steel factor is c-Kit receptor ligand, and is necessary for the development and survival of ICC. In the absence of steel factor these cells transdifferentiate into smooth muscle cells or fibroblast like cells (32).

Shimoima et al. (33) and Suzuki et al. (34) showed decrease in c-Kit positive cells around the myenteric twelve hours after ischemia-reperfusion injury of the small intestine in rats, and also recovery of c-Kit positivity four days after. Chang and colleagues (35) reported that after experimentally induced partial occlusion of the ileum of mice, there is a decrease in the number of ICC-MY, proximal to the occlusion site, with disruption of the ICC network and consequent intestinal dysmotility. The release of pro-in-flammatory cytokines and chemokines has a negative effect on the number and function of nearby ICC, leading to damage to their network and dysfunction (36). With the absence of harmful factors, the number of ICC can recover and re-establish their network. Two mechanisms of ICC renewal have been proven. One is the differentiation from a small group of cells with weak c-Kit immunoreactivity (CD 117+), and pronounced CD 44+, CD 34+ immunoreactivity, which may represent a source of precursor cells for ICC renewal (37). Another mechanism is proliferation, and there is evidence that steel factor, NO from neurons, serotonin (via the 5HT28 receptor) and heme oxygenase-1 can induce proliferation of ICC (38). It is the potential of ICC restoration that may represent a potential therapeutic approach in diabetic enteropathy that should be further investigated.

Identifying cellular biomarkers may help us in developing better strategies for the diagnosis and management of the diabetic enteropathy. ICC as biomarkers could be linked to the treatment outcome and prognosis in these patients.

Conclusion

In conclusion, a statistically significant decrease in the number of intramuscular ICC and myenteric ICC was observed in all examined parts of the small intestine in rats with diabetes mellitus. Diabetes mellitus significantly changes the microenvironment of ICC and most likely affects the reduced signaling by insulin, thereby affecting the loss of ICC.

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GUBITAK INTERSTICIJALNIH ĆELIJA KAHALA U TANKOM CREVU PACOVA SA DIJABETESOM MELITUSOM

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Dijabetička gastroenteropatija predstavlja čestu komplikaciju dijabetesa melitusa. Poremećaj zastupljenosti intersticijalnih ćelija Kahala (IĆK) ima značajnu ulogu u patogenezi intestinalnih poremećaja motiliteta.

Cilj ove studije bio je da odredi distribuciju intramuskularnih i mijenteričnih IĆK u tankom crevu pacova sa dijabetesom melitusom.

Dijabetes melitus izazvan je streptozotocinom i nikotinamidom na animalnom modelu Wistar pacova muškog pola. Imunohistohemijsko ispitivanje vršeno je c-kit antitelom za identifikaciju IĆK. Zastupljenost intramuskularnih IĆK određivana je numeričkom arealnom gustinom, dok je za procenu mijenteričkih IĆK korišćen ICC-skor. Rezultati studije pokazali su smanjenje broja IĆK i njihovog umrežavanja u tankom crevu u grupi pacova sa dijabetesom.

Statistički značajan gubitak broja intramuskularnih i mijenteričnih IĆK zapažen je u svim uzorcima tankog creva pacova sa dijabetesom melitusom. Dijabetes značajno menja mikrookolinu IĆK i, najverovatnije, smanjenom signalizacijom preko insulina utiče na njihov opstanak.

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***Ključne reči**: intersticijalne ćelije Kahala, dijabetes melitus, tanko crevo, gastroenteropatija*

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IMPACT OF ANDROGEN DEPRIVATION THERAPY AND OPEN RADICAL RETROPUBIC PROSTATECTOMY ON LOWER URINARY TRACT SYMPTOMS IN PATIENTS WITH PROSTATE CANCER

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The aim of this study was to show the impact of open radical prostatectomy (ORP) and primary hormone therapy on lower urinary tract symptoms (LUTS) and quality of life (QoL) related to these symptoms based on the International Prostate Symptom Score (IPSS).

A total of 128 patients with localized prostate cancer were analyzed and divided into two groups. The first group consisted of subjects who underwent ORP, and the second group consisted of subjects who were primarily treated with hormone therapy for 12 months. To assess the impact of ORP and hormone therapy on LUTS and QoL, the IPSS and IPSS QoL questionnaires were used before the start of treatment and after 3, 6 and 12 months from the start of treatment.

In both groups of subjects, the IPSSt score consistently significantly decreased during the follow-up period compared to the baseline ($p < 0.001$ for all). After 12 months IPSSt and IPSSv were significantly higher in group with hormonal therapy compared to ORP group ($p < 0.001$) and IPSSs was significantly higher ORP group compared to hormonal therapy group. In both groups of subjects, IPSS QoL consistently decreased significantly during the follow-up period ($p < 0.001$). IPSS Qol was significantly higher in ORP group compared to hormonal therapy group at baseline ($p < 0.001$), after 3 months ($p=0.003$), after 6 months ($p = 0.002$).

ORP and hormone therapy as the primary treatment methods for patients with localized PC led to a statistically significant decrease in IPSS scores and a clinically significant improvement in LUTS. Also, QoL related to LUTS significantly improved in both groups of subjects after 12 months.

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Key words: *hormone therapy, prostate cancer, radical prostatectomy, urinary symptoms*

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Introduction

Prostate cancer (PC) is the second most frequently diagnosed cancer among men worldwide (1), and in Serbia it is the leading malignant neoplasm after lung cancer. Localized PC is an indication for radical prostatectomy (RP), radiation therapy, or active surveillance (2). In recent years, primary hormone therapy has gained popularity in the treatment of localized PC. Although no randomized control studies that would compare hormone therapy with other therapeutic options in localized PC have been published (3), according to literature data, this method of treating localized PC is becoming the second most common method of treatment after RP (4). In the majority of men, cancer develops from the peripheral zone of the prostate, causing local symptoms, and when growth involves or compresses proximal structures such as the prostatic urethra, urinary bladder or neurovascular bundles, lower urinary tract symptoms (LUTS) appear (5). Also, with the development of PC, prostate volume also increases due to benign hypertrophy, the prevalence of which increases with age, which is another reason for the occurrence of lower urinary tract symptoms (LUTS) (6). PC is a hormone-dependent neoplasm, so it can be effectively treated with agents that either block androgen receptors or reduce

testosterone production (6). Androgen deprivation therapy (ADT) is both cytotoxic and cytostatic for hormone-sensitive PC cells and therefore has a strong effect on tumor growth and viability (7), which consequently leads to a reduction in both prostate and tumor volume and can alleviate LUTS symptoms in patients with PC. Following RP, there is a temporary disturbance of the function of the lower urinary tract in the early phase after the operation, which is a consequence of the removal of the prostate and the subsequent reanastomosis of the urethra and bladder neck (2). Several studies have reported the effect of open RP (ORP) on LUTS (8, 9, 10), however, almost no studies have reported the effect of hormone therapy on LUTS in patients with localized PC, nor a comparison of the effect of these two treatment modalities on LUTS in localized PC.

We investigated and compered effects of 12-month hormone therapy and ORP on LUTS and LUTS-related quality of life (QoL) using the International Prostate Symptom Score (IPSS).

Material and methods

A prospective clinical study was conducted in the period from January 2016 to March 2021 in which 128 patients with histologically proven PC in clinical stage ≤ T2 participated. In the first group, there were 64 patients who underwent ORP with a modified approach described by Walsh. Another 64 patients in the second group underwent primary hormone therapy with an LHRH (luteinizing hormone-releasing hormone) agonist, with quarterly doses for 12 months. Respondents from this group refused operative treatment (ORP) even if this method of treatment was proposed to them as primary. Urinary incontinence and erectile dysfunction as possible complications after ORP were the reason for not accepting operative treatment.

All respondents were informed about the objectives of the research and signed their consent to participate in the research. The study was conducted at the Clinic of Urology and Clinic of Oncology in the University Clinical Center Niš. The basic inclusion criteria in the study were: value of prostate specific antigen (PSA) < 40 ng/ml, verification of PC by transrectal biopsy, assessment of the clinical stage of the disease up to T2c stage, Gleason score (GS) ≤ 9. Basic data analyzed for both groups were: age, PSA, GS, clinical stage, level of serum hemoglobin, urea (Ur), creatinine (Cre) and the American Society of Anesthesiologists (ASA) score. The International Prostate Symptom Score (IPSS) questionnaire was used to assess the impact of applied treatment methods on LUTS and urination quality. LUTS was assessed on the basis of the IPSS (IPSSt) and the IPSS QoL score. The IPSS is a self-administered seven-item questionnaire comparing items of incomplete emptying, intermittency, straining, weak stream (voiding symptoms) and voiding frequency, nocturia, and urgency (storage symptoms). Each scale is scored separately from 0 to 5, with a higher score indicating a worse symptom. The IPSS is scored from 0 to 35 in all, with scores of 0–7, 8–19, and 20–35 indicating absent or mild, moderate, and severe symptoms, respectively (11). The IPSS QoL score is a questionnaire that quantifies the QoL for LUTS and is scored from 0 to 6, with a higher score representing a worse health state. A cut-off IPSS score of 7 points was used to determine the number of patients who significantly improved voiding quality. All patients included in the study filled out both questionnaires before surgery and before the start of hormone therapy and in the third, sixth and twelfth months after the start of treatment. Voiding symptom composites (IPSSv) and storage symptom composites (IPSSs) were analyzed independently. All procedures on human subjects were done in accord with the ethical standards of Helsinki Declaration.

Results

Demographic and clinical characteristics are presented in Table 1. Patients who underwent hormone therapy were statistically significantly older than patients who underwent ORP ($p < 0.001$). A statistically significant difference between the two groups was in the results of GS on biopsy ($p = 0.003$).

A repeated-measures ANOVA indicated a significant time x group interaction for IPSSt, IPSSv, and IPSSs ($p < 0.001$ for all). In both groups of subjects, the IPSSt score consistently significantly decreased during the follow-up period compared to the baseline ($p < 0.001$ for all). At baseline, 3 months and 6 months, IPSSv and IPSSs were significantly different between groups ($p < 0.001$ for all) (Table 2). Three months after ORP, IPSSs significantly increased compared to the baseline ($p < 0.001$), and then from the 6th month it did not differ significantly compared to the period before surgery ($p > 0.05$ for all). In the hormone group, IPSSs did not differ significantly between measurements ($p > 0.05$ for all). After 12 months IPSSt, IPSSv and IPSSs were significantly higher in patients with hormonal therapy compared to ORP group ($p < 0.001$). After 12 months IPSSt and IPSSv were significantly higher in patients with hormonal therapy compared to ORP group ($p < 0.001$) and IPSSs was significantly higher in patients after ORP compared to hormonal therapy group (Table 2).

Analysis of IPSS Qol showed a significant time x group interaction ($p = 0.010$). In both groups of subjects, IPSS QoL consistently decreased significantly during the follow-up period ($p < 0.001$). IPSS Qol was significantly higher in patients with ORP compared to hormonal therapy at baseline ($p < 0.001$), after 3 months ($p = 0.003$), after 6 months ($p = 0.002$) (Figure 1).

Before the start of treatment, the number of subjects with IPSSt score ≤ 7 was equal (26.6% and 17.2%, respectively, $p = 0.285$) (Figure 2).

After 3, 6 and 12 months there were no subjects on hormone therapy with IPSSt ≥ 20, and after 6 and 12 months in the group after ORP. After 12 months from ORP, 38 patients (59.4%) moved to the category IPSSt ≤ 7. Comparing the same period, 1 patient moved to the category IPSSt ≤ 7 and one patient (1.6%) moved to the category IPSSt > 7 in the hormone therapy group. There was significant difference in IPSS categories between treatment group after 3 months ($p = 0.003$), 6 months ($p < 0.001$), and 12 months ($p < 0.001$). Comparing the baseline values with the period after 12 months, it was determined that 16 patients (25.0%) had and maintained an IPSSt score ≤ 7, 46 patients (71.9%) had and kept an IPSSt score > 7, and one patient moved to a lower and a higher category (1.6% each) in the hormone therapy group (Figure 2). Within the same time interval in ORP group, it was found that 11 patients (17.2%) had and maintained an IPSSt score ≤ 7, 12 patients (18.8%) had and maintained an IPSSt score > 7, and 41 patients (64.1%) moved to a lower score category.

Table 1. Baseline demographic and clinical characteristics of population

Characteristics	**RRP**		**Hormonal Therapy**		**p**
Age	64.3 ± 4.0	53-71	67.3 ± 4.7	61–72	0.002[1]
Ur (mmol/l) before treatment †	6.1 ± 1.0		5.7 ± 1.3		0.053[1]
Ur (mmol/l) 3, month †	5.7 ± 1.2		5.8 ± 1.2		0.638[1]
Cre (mmol/L) before treatment†	94.7 ± 16.4		93.1 ± 17.4		0.593[1]
Cre (mmol/L) 3, month †	91.5 ± 15.3		94.6 ± 16.2		0.269[1]
Hemoglobin (g/L)†	125.7 ± 16.0		123.0 ± 14.5		0.319[1]
Hemoglobin (g/L)†	127.2 ± 14.1		123.0 ± 12.1		0.073[1]
Clinical stage					
T2 a, b	57	89.1	55	85.9	0.593[2]
T2c	7	8.9	9	14.1	
Gleason score on biopsy					
≤ 6	37	57.8	31	48.4	0.003[3]
7	20	31.2	17	26.6	
8	7	11.0	15	23.4	
9	0	0.0	1	1.6	
Basic PSA, (ng/ml) †	10.9 ± 5.1	1.6-23.2	20.0± 11.0	3.6-38.6	< 0.001[4]
ASA score					
0	6	9.4	1	1.6	0.052[2]
1	7	10.9	14	21.8	
2	51	79.7	49	76.6	
Pathological stage					
T1	1	1.6			
T2a,b	55	85.9			
T2c	8	12.5			0.742*[2]
Pathological Gleason score					
≤6	30	46.9			
7	24	37.5			
8	9	14			0.097*[2]
9	1	1.6			

Data are presented as n or (%); † Mean ± standard deviation, Min-Max.; ASA = American Society of Anesthesiologists; * Comparison of stage and GS in the RP group, 1 Student's t-test, 2 Chi-Square test, 3 Fisher's exact test, 4 Mann-Whitney U test.

Table 2. IPSS scores in patients with hormonal and RRP therapy

		Baseline	**After 3 months**	**After 6 months**	**After 12 months**	**p**
IPSSt	Hormonal th	12.41 ± 4.86	10.09 ± 3.39	9.23 ± 2.54	9.08 ± 2.5	< 0.001[1] < 0.001[2] < 0.542[3]
	ORP	11.98 ± 4.57	10.45 ± 4.72	9.53 ± 3.7	7.41 ± 2.56	
IPSSv	Hormonal th	8.22 ± 3.56	5.94 ± 2.32	4.97 ± 1.78	4.84 ± 1.75	< 0.001[1] 0.003[2] < 0.001[3]
	ORP	6.02 ± 2.85	3.38 ± 3.27	3.36 ± 2.44	1.91 ± 1.41	
IPSSs	Hormonal th	4.19 ± 1.59	4.16 ± 1.35	4.27 ± 1.16	4.23 ± 1.16	< 0.001[1] < 0.001[2] < 0.001[3]
	ORP	5.97 ± 1.98	7.08 ± 1.83	6.17 ± 1.74	5.5 ± 2.02	

[1] time effect, [2] interaction time x group, [3] group effect.

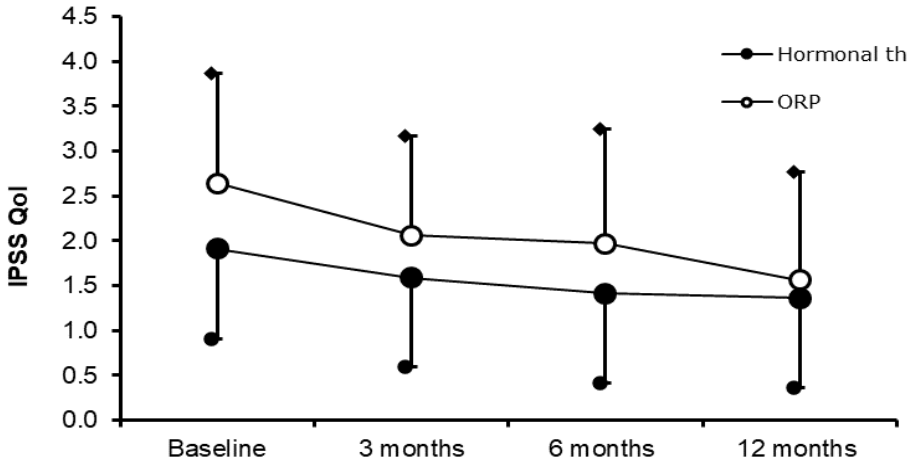

Figure 1. IPSS QoI in patients with hormonal therapy and ORP therapy in the 12-month follow-up

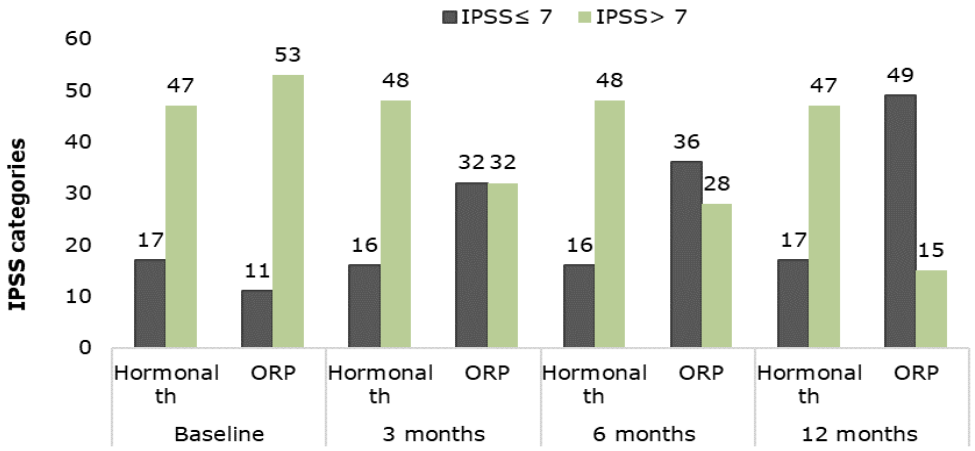

Figure 2. IPSS categories in the 12-month follow-up period

Discussion

Our results showed a positive influence of both hormonal therapy and ORP with LUTS, as a statistically significant improvement of the mean IPSSt compared to the baseline value was verified in each of the follow-up time intervals after 12 months. It is the nature of PC to react to hormones, so the application of ADT has a cytostatic and cytotoxic effect on PC cells and thus on the growth and viability of the tumor (7). Similar results to ours were published by other authors (6, 12).

Choi et al., analyzing the effect of ADT on total prostate volume and LUTS, concluded that after 12 months from the beginning of this therapy, there was a significant reduction in average prostate volume, average IPSSt, IPSSv and IPSSs (12). The average prostate volume decreased from 36.6 ± 14.6 to 19.4 ± 12.4 ml in 51.1% of treated patients, IPSSt from 17.4 ± 8.5 to 12.2 ± 7.6, IPSSv from 9.8 ± 6.1 to 6.7 ± 5.1, and IPSSs from 7.6 ± 3.7 to 5.5 ± 3.5 points after 12 months (12). They also showed an average 1-point improvement in IPSS QoL (4.0 ± 1.9 vs. 3.2 ± 0.9) and an improvement in maximum urine flow of 3 ml/s. However, in patients who continued to receive hormonal therapy, the values of these parameters did not change significantly compared to the results after 12 months. In relation to the mentioned study, in our research a significantly smaller average decrease in both IPSSt and IPSSv and IPSS QoL was verified after 12 months, which can be explained by the significantly lower baseline values of these scores compared to the previous study. We did not verify a drop in the average values of IPSSs until the end of the follow-up and in relation to the compared results, in our patients the basic average value of this

score was almost twice as low (4.19 ± 1.59 vs. 7.65 ± 3.75) (12), so we can assume that this is one of the reasons for this obtained result. Another study showed similar results for all IPSSs after a follow-up of 24 weeks and did not verify significant changes in IPSSs (6).

Regardless of the statistically significant overall decrease in mean IPSSt after 12 months, our results verified only one patient (1.6%) who moved to a lower category IPSSt ≤ 7 and one patient who moved to the category IPSSt > 7 which is significantly less compared to the ORP group. Despite the use of ADT, in a certain number of patients LUTS may persist, progress and often lead to acute or chronic development of retention. Several studies have confirmed that half of patients who started ADT with severe LUTS or had an indwelling urinary catheter still had severe symptoms at 12 months, and half still have an indwelling catheter (6, 13).

Of course, hormone therapy leads to a reduction in the volume of the prostate and tumors, so this can explain the improvement in LUTS in patients with PC (6). These clinical effects may be explained by another potential mechanism. Namely, receptors for gonadotropic releasing hormone are located on smooth muscle cells of the bladder neck and prostate. Indirect effects of testosterone deprivation by pituitary receptors can favorably affect the static and dynamic components responsible for bladder emptying (14, 15). Blockade of receptors on these cells is associated with a decrease in pro-inflammatory cytokines, various growth factors and alpha adrenoreceptors (16). Therefore, reduction of prostate volume under the effect of ADT is not the only mechanism that can improve LUTS and voiding quality. Changes in the tissues of the prostate and bladder under the effect of ADT can cause additional morbidity of the urinary tract, which results in the appearance of irritative and obstructive symptoms that patients with PC complain about.

Although both treatment methods showed a positive impact on reducing LUTS and improving LUTS-related QoL, this impact was significantly greater in patients after ORP. Analysis of the results of ORP on LUTS showed that only men with clinically significant urinary symptoms (IPSSt > 7) could benefit from ORP, because IPSSt significantly decreased after 12 months and urinary quality improved. In a study similar to ours (10), the authors analyzed the results of IPSSt, IPSSv,IPSSs and IPSS QoL in 254 men who were divided into three groups (IPSS < 8, IPSS 8-19 and IPSS 20+) 12 months after ORP. The results of this study showed a statistically significant decrease in the mean values of IPSSt, IPSSv and IPSS QoL scores, which was also confirmed by our results (10). The results of the mentioned study showed a significant drop in the mean value of IPSSt after 12 months (10), but by almost 50% compared to our results (2.3 vs. 4.57). The reason for this difference in IPSSt values is the consequence of the basically lower mean value of IPSSt in the mentioned study compared to ours (10.69 ± 4.88 vs. 11.98 ± 4.57). Also, the same authors confirmed the improvement of QoL related to urinary symptoms after ORP, because IPSS QoL after 12 months improved on average by 0.5 points (10), and in our study this improvement was on average by 1 point (2.64 vs. 1.56). This minimal difference is the result of the basically lower mean IPSS QoL value obtained in the mentioned study in comparison to our result (1.95 vs. 2.64).

Slova and Lepor analyzed the results of IPSSt, IPSSv and IPSSs 12 and 48 months after RP (9). They showed a significant decrease in mean IPSSv at 12 months, but not IPSSt. Contrary to the results of these authors, our results showed a statistically significant decrease in mean IPSSt values after 12 months. The reason for this discrepancy can be explained by the existence of a basically higher mean value of IPSSt (11.98 vs. 6.9) and a greater number of patients operated with IPSS > 7 (73.5 vs. 50.4%) in our study compared to the mentioned study. Also, the authors showed a significant decrease in the mean values of IPSSt and IPSSv after 48 months. The improvement in LUTS and decrease in mean IPSSt was attributed primarily to a decrease in mean IPSSv in the first 12 months and a decrease in IPSSs in the period 12−48 months after surgery (9). And our results after 6 and 12 months after ORP showed a significant decrease in the mean values of both IPSSv and IPSSt, which suggests or justifies the role of IPSSv in the improvement.

On the other hand, we could not assess whether the results of IPSSs positively or negatively influenced IPSSt after 12 months because the mean values of IPSSs preoperatively and after 12 months remained approximately the same (5.9 vs. 5.5). Similar results for the same follow-up time interval were presented by the authors in the above-mentioned study (4.2 vs. 4.5) (9). Also, they showed a statistically significant decrease in the mean value of IPSSs after 48 months compared to 12 months (9), which we did not follow in our research. After 6 and 12 months of ORP, a significant improvement in LUTS was observed, which resulted in a significant decrease of the mean IPSSt by 2.5 and 4.5 points compared to the baseline value. We believe that this improvement in LUTS mainly occurred in patients who had a baseline IPSSt > 7 (82.8%), as there was a significant decrease in the number of patients in this category after 6 (43.8%) and 12 months (23.4%). Results from other studies have also shown improvement in LUTS after RP in men with IPSS ≥ 8 (9, 17).

Bayoud and colleagues analyzed LUTS in 804 men after RP (18). They showed a significant increase in the mean value of IPSSt after the 1st and 3rd month (11.1 ± 7.1 vs. 7.6 ± 6.1) compared to the baseline value (5.5 ± 6.6), and in the 6th, 12th and 24th month they found no statistically significant difference (18). Contrary to the above, our results showed a slight decrease in the mean value of IPSSt in the 3rd month (11.9 ± 4.5 vs. 10.5 ± 4.7) with a gradual decrease in the

6th and 12th months. This difference in the downward trend of the mean IPSSt can be explained by the very high basic IPSSt in relation to the observed study and the larger number of patients who had IPSSt > 7 (82.8% vs. 34.5%). The authors also showed a decreasing trend in the number of patients in the IPSS > 7 subgroup: 42.4%, 32.9%, 21.7% and 17% after 3, 6, 12 and 24 months, respectively (18), which we also confirmed in the 3rd, 6th and 12th months (50.0%, 43.8% and 23.4%) after ORP. The beneficial role of RRP on LUTS is also discussed in a study by Papadopoulos and colleagues who analyzed 240 men after RRP (19). Analyzing maximal urine flow rate (Qmax) and IPSS, their results showed an increase in median Qmax after 12 months from 12 to 21 ml/s in patients who had Qmax ≤ 10 ml/s at baseline, and a significant decrease in IPSSt in the groups of patients with baseline moderate and severe urination symptoms (19).

Analyzing QoL as a consequence of LUTS after ORP, our results showed a significant improvement in IPSS QoL after 12 months with a significant difference compared to baseline (2.6 ± 1.2 vs. 1.5 ± 1.2), and thus the positive impact of operative treatment on IPSS QoL. We also observed that changes in IPSS QoL mean values directly correlated with improvement and worsening trends in LUTS and IPSSt after ORP. Similar results were published by other authors (20, 21). Mastubara et al. showed a significant improvement in IPSSt and IPSS QoL after 3, 6 and 12 months of RRP, especially in those patients operated with a baseline IPSSt ≥ 8 (20).

Schwartz et al. showed a significant improvement in all urinary symptoms except nocturia after 12 months of RRP and an improvement in IPSS QoL regardless of the 10% of patients who had severe urinary incontinence (21). They concluded that the majority of patients who had undergone RRP were satisfied with their choice of treatment method and that the improvement in IPSS QoL and IPSSt had a more significant positive impact on patients than the negative impact of urinary incontinence (21).

Several authors have studied the negative impact of RRP on LUTS, and the basis of the hypothesis of this phenomenon is damage to the pelvic plexus, a lesion of nerves from the neurovascular bundle during surgical dissection (20, 22, 23). *De novo* incontinence and an increase in the frequency of day and night urination are associated with the resulting weakness of the sphincter, which impairs the filling and emptying phases of the bladder (20, 22, 23). In addition to the positive impact, our results also showed a negative RRP on IPSSt QoL in the five operated patients, which is probably a consequence of some degree of incontinence and occurrence of nocturnal urination, which we did not analyze in this research. This observation of ours was confirmed by other authors (23). After 3, 6, 12, and 24 months of RRP, Namiki et al. showed statistically significant improvements in IPSSt and IPSS QoL at 6 postoperative months, but after 24 months, 26% of those operated on reported having worsening LUTS (17). The reason for this was the occurrence of nocturnal urination in the operated patients who, preoperatively, did not or only got up once to urinate at night. They suggest that nocturia is due to detrusor contractility disorders and sphincter weakness as a consequence of surgery (17). Our study has several limitations. This is not a randomized control trial. Assessment of the impact of ORP and hormone therapy on LUTS is subjective. Assessment of urinary symptoms is based on IPSS and IPSS QoL questionnaires. On the other hand, the results of the impact of hormone therapy lasting 12 months on LUTS in patients with localized PC are shown, which has not been published in the literature so far.

Conclusion

ORP and hormone therapy as the primary treatment methods for patients with localized PC led to a statistically significant decrease in IPSS scores and a clinically significant improvement in LUTS. Also, QoL related to LUTS significantly improved in both groups of subjects after 12 months. We observed that in patients with moderate to severe LUTS, ORP led to a clinically significant improvement in LUTS compared to primary hormone therapy.

Acknowlegments

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UTICAJ ANDROGENE DEPRIVACIONE TERAPIJE I OTVORENE RADIKALNE RETROPUBIČNE PROSTATEKTOMIJE NA SIMPTOME U DONJEM URINARNOM TRAKTU KOD BOLESNIKA SA KARCINOMOM PROSTATE

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Cilj ove studije bio je da se prikaže uticaj otvorene radikalne prostatektomije (engl. *open radical prostatectomy* – ORP) i primarne hormonoterapije na simptome donjeg urinarnog trakta (engl. *lower urinary tract symptoms* – LUTS) i na kvalitet života (engl. *quality of life* – QoL) u vezi sa ovim simptomima na osnovu Internacionalnog prostata simptom skora (engl. *International Prostate Symptom Score* – IPSS).

Analizirano je 128 bolesnika sa lokalizovanim karcinomom prostate, podeljenih u dve grupe. Prvu grupu činili su ispitanici koji su podvrgnuti ORP-u, a drugu grupu ispitanici koji su primarno lečeni hormonoterapijom u trajanju od dvanaest meseci. Za procenu uticaja ORP-a i hormonoterapije na LUTS i QoL korišćeni su upitnici IPSS i IPSSQoL, i to pre početka lečenja i nakon tri meseca, šest meseci i dvanaest meseci od početka lečenja.

U obema grupama ispitanika IPSSt skor konstatno se statistički značajno smanjivao u periodu praćenja u odnosu na bazičnu vrednost ($p < 0,001$ za sve). Nakon dvanaest meseci, IPSSt i IPSSv bili su značajno veći u grupi na hormonoterapiji nego u ORP grupi ($p < 0,001$), a IPSSs je bio značajno veći u ORP grupi nego u grupi bolesnika lečenih hormonoterapijom. U obema grupama ispitanika IPSSQoL se konstatno značajno smanjivao u periodu praćenja ($p < 0,001$). IPSSQoL je bio značajno viši u ORP grupi nego u grupi bolesnika lečenih hormonoterapijom, i to pre početka lečenja ($p < 0,001$), nakon tri meseca ($p = 0,003$) i nakon šest meseci ($p = 0,002$).

ORP i hormonoterapija su kao primarne metode lečenja bolesnika sa lokalizovanim PC-om dovele do statistički značajnog pada IPSS skorova i klinički značajnog poboljšanja LUTS-a. Takođe, QoL u vezi sa LUTS-om značajno se popravio nakon dvanaest meseci u obema grupama ispitanika.

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***Ključne reči**: hormonoterapija, karcinom prostate, radikalna prostatektomija, urinarni simptomi*

Case report

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HOW TO PERFORM SAFE RETROGRADE CHRONIC TOTAL OCCLUSION RECANALIZATION

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Chronic total occlusion (CTO) of the coronary artery is defined as more than three-month-old total (100%) anterograde flow obstruction in the native coronary artery.

The data show that 7% – 15% of CTOs are treated with percutaneous coronary intervention and that CTO recanalization still represents the cutting edge in percutaneous coronary intervention. Three different techniques for the CTO recanalization have been described in the literature: antegrade wire escalation, antegrade dissection/re-entry, and retrograde. In case of multiple possibilities for selection of collateral channels, the septal group still represents the most common choice in a large number of retrograde CTO interventions because of the lowest major complication rate. Septal perforations are generally not followed by serious complications and usually resolve spontaneously. On the other hand, epicardial collateral channels can be used with a high rate of success and low incidence of procedural complications when revascularization procedures of CTO lesions are performed by experienced interventional cardiologists and high-volume laboratories.

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Key words: *chronic total occlusion, percutaneous coronary intervention, collateral channels*

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Introduction

Chronic total occlusion (CTO) of the coronary artery is defined as more than three-month-old total (100%) anterograde flow obstruction in the native coronary artery. The frequency of a CTO has been reported to be up to 30% among patients with a clinical indication for coronary angiography. The data show that 7% – 15% of CTOs are treated with percutaneous coronary intervention (PCI) and that CTO recanalization still represents the cutting edge in percutaneous coronary intervention (1).

Until today, three different techniques for the CTO recanalization have been described in the literature: antegrade wire escalation, antegrade dissection/re-entry, and retrograde (2, 3). Using the antegrade approach, success rates have been limited between 60% and 70%. However, with the equipment and techniques improvement, some serious progress has been made in this sensitive field. Thanks to the vast knowledge and considerable expertise, retrograde techniques have become a crucial complement to the treatment of CTO. Retrograde approach to CTO percutaneous coronary intervention was first mastered and introduced by Japanese surgeons thanks to whom new perspectives regarding the use of small collateral channels (CCs) were opened. There are a few types of CCs: septal, epicardial, atrial and vein grafts (after cardiac bypass surgeries). Septal CCs are the safest and should be the primary choice whenever possible because the epicardial rupture is more serious than the septal rupture. Since the use of epicardial CCs may be associated with procedural ischemia, these CCs should be used only if no septal CCs are suitable (4).

Case presentation

First attempt in General Hospital Zaječar

Procedure: JL guiding catheter (Judkins left) 4.0 6 French (Launcher, Medtronic, Minneapolis, MN, USA) was engaged in the left main trunk of the left coronary artery. Over Runthrough Floppy wire (Terumo, Japan), Microcatheter Finecross

(Terumo, Japan) was placed in front of the proximal cap of CTO. With the wire escalation technique, Progress 40 (Abbott, Santa Clara, USA) and Confianza Pro 9 (Asahi Intecc, Japan), the procedure failed. We could not open the chronic total occluded left anterior descending coronary artery (LAD) (Figure 1) with an antegrade approach because wires always went to the first diagonal branch. Consequently, we put the balloon in the ostium of this diagonal branch to prevent and block the entering of wires. We planned a retrograde approach in Clinical Center Niš over epicardial homo-collateral (septal collaterals from RCA did not exist).

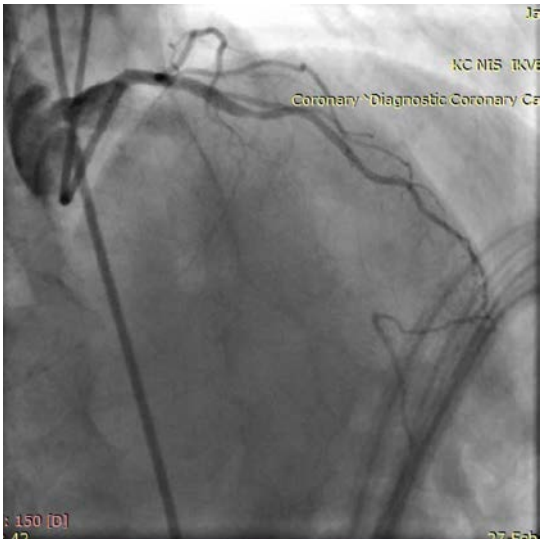

Figure 1. LAD occlusion

Second attempt in Clinical Center Niš

Procedure: In this attempt, the retrograde approach was planned as a first-line strategy. EBU (Extra backup) 3.75 7F (French) was placed in the left coronary artery. Over the standard Floppy wire, we went to the first diagonal branch with Finecross (Terumo, Japan) microcatheter to examine the possibilities for a retrograde approach. We started with Sion wire (Asahi Intecc, Japan) and went very easily through this epicardial collateral to the distal cap of CTO (Figure 2). This wire penetrated the distal cap of LAD CTO. Then, we went further down over Sion with a Finecross microcatheter to give support for further wires. Sion went very close to the proximal cap (sliding to septal in the proximal part of CTO), but could not penetrate it. We switched Sion through Finecross for Ultimate Bros 3 (Asahi Intecc, Japan) and Pilot 200 (Abbott Vascular, USA), but those wires could not cross the proximal CTO segment. Finally, Progress T 140 crossed the CTO but finished in the subintimal space and could not reenter into the proximal true lumen. To minimize the dissected proximal segment, we exchanged the last stiff wire—Confianza Pro 12 (Asahi Intecc,

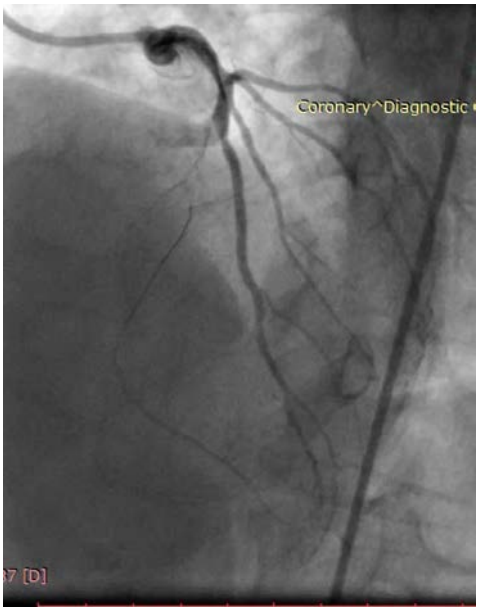

Figure 2. Retrograde wire crossing

Japan) for Runthrough Hypercoat (Terumo, Japan). After that, we switched to antegrade preparation for the reverse cart. With Finecross support, coronary wire Progress 200 T (Abbott Vascular, Santa Clara, CA) went through the proximal CTO cap and allowed antegrade balloon inflations in reverse cart technique (Figure 3). First, we removed antegrade Finecross using the trapping balloon technique and the advanced smallest monorail coronary balloon Sprinter Legend 1.25 x 15 mm, then bigger Sprinter Legend 2.5 x 15 mm. After a few inflations of 2.5 mm balloon, retrograde wire Sion Blue (Asahi Intecc, Japan) went to the proximal true lumen. Suddenly, the occurrence of ventricular fibrillation was noted. During short resuscitation and defibrillation with 360 J, the guiding catheter and both coronary

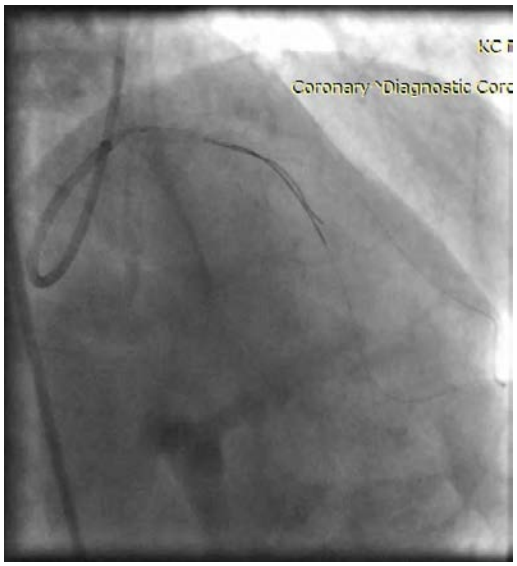

Figure 3. Reverse CART

wires (antegrade and retrograde) lost previous positions. When the patient's hemodynamic condition was stabilized, we used again guiding catheter and two wires and tried to cross the CTO segment antegradely into the true lumen in LAD and first diagonal branch—Balance Middle Weight (BMW) (Abbott Vascular, Santa Clara, USA) and Whisper ES (Abbott Vascular, Santa Clara, USA). After successful wiring of distal LAD, several predilatations were performed in the occluded segment with Maverick Monorail 3.0 x 20 mm (Figure 4) (Boston Scientific Corporation, USA). We put two BioMime sirolimus-eluting stents (SES)(Meril Life Sciences Pvt. Ltd., Gujarat, India) 3.0 x 29 mm (Figure 5) in the distal and 3.5 x 19 mm (Figure 6) in the proximal part of CTO to cover dissection caused by the ret-rograde system. After the implantation of the three SES, we achieved TIMI 3 flow in LAD. Finally, we found a very small dissection at the end of the distal stent, but we were satisfied with the angiographic result and finished the procedure (Figure 7, Figure 8).

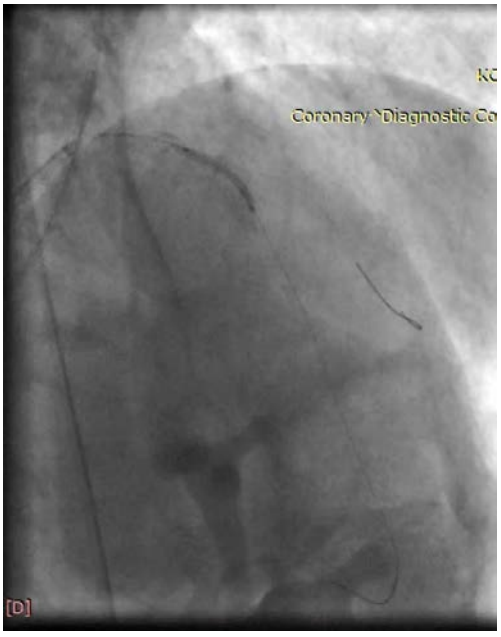

Figure 4. Balloon predilatation

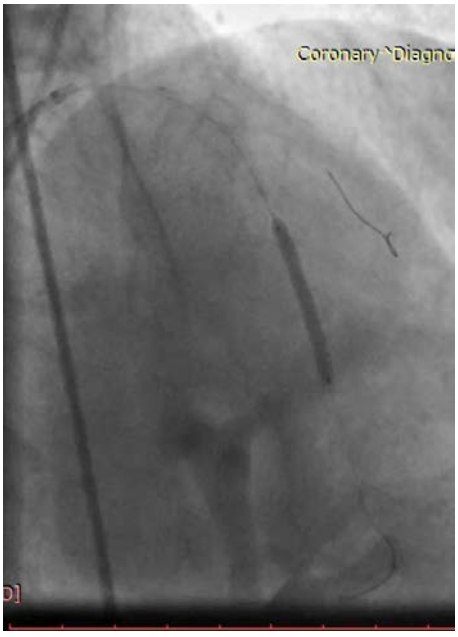

Figure 5. Stent implantation

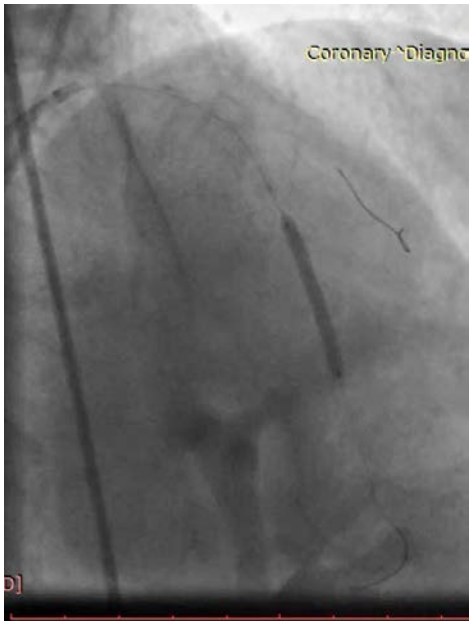

Figure 6. Stent implantation

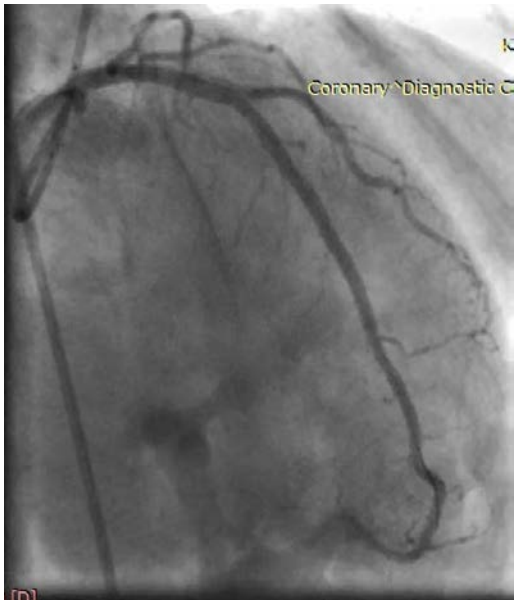

Figure 7. Final result

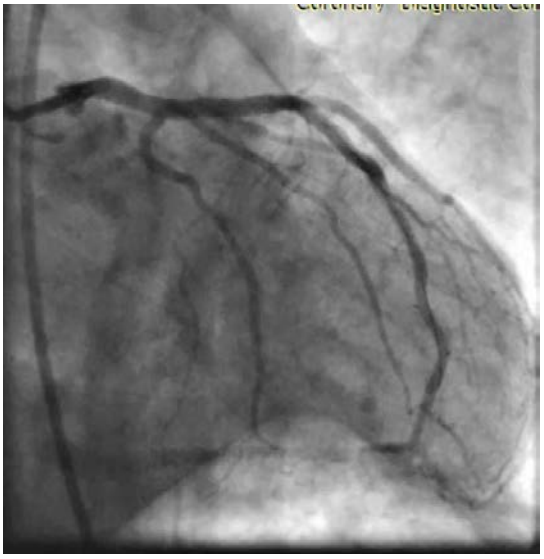

Figure 8. Final result

Discussion

Despite the continuing improvement of percutaneous coronary intervention materials, technical expertise and equipment, the treatment of CTO lesions still represents a challenge for interventional cardiologists in current clinical practice (5, 6). Because of procedural complexity, CTO interventions are associated with a higher risk of complications and lower success rates (60%–70%) in comparison with PCI of nonoccluded or acutely occluded vessels (2, 7). Also, restenosis rates are high even in successful cases of CTO recanalization (8). The most commonly described complications which may occur during PCI of CTOs are coronary perforation which can be associated with cardiac tamponade, coronary dissection due to aggressive guide manipulation, periprocedural myocardial infarction, device embolization, systemic embolization, side branch occlusion, renal dysfunction (contrast induced nephropathy), and radiation dermatitis (6, 7). However, despite all disadvantages, successful recanalization of CTOs can reduce angina symptoms and need for coronary artery bypass graft surgery in appropriately selected patients with documented viable myocardium. Besides, in these patients successful PCI of CTOs is also associated with improvement of left ventricular function, increased exercise tolerance, decreased incidence of myocardial infarction, reduced risk of arrhythmic events as well as improvement of long-term survival (2, 3, 9).

In case of multiple possibilities for the selection of collateral channels, the septal group still represents the most common choice in a large number of retrograde CTO interventions because of the lowest major complication rate (10). Septal perforations are generally not followed by serious complications and usually resolve spontaneously. However, in some cases, septal perforations may lead to the occurrence of ventricular dysrhythmias or septal haematoma which can cause hypotension due to obstruction of the left ventricular outflow tract (11, 12). As opposed to septal collaterals, retrograde approach to CTO percutaneous coronary intervention through an epicardial vessel carries an increased risk of vessel perforation during the wire manipulation which can rapidly cause pericardial tamponade. Likewise, cardiac tamponade can occur as a result of epicardial collateral rupture due to balloon dilatation. According to that, dilatation of these collaterals should be avoided. However, in patients who have undergone coronary artery bypass grafting (CABG), the chance for pericardial tamponade is lower because the pericardial space has been accessed before. Nevertheless, local chamber compression can still occur in these patients (12).

Conclusion

Nowadays, CTO recanalization is considered to be the most modern method in the field of interventional cardiology. The presence of severe tortuosities, fibrous and calcified material, and large bifurcations may represent aggravating circumstances for the surgeon and therefore adequate assessment of lesions and appropriate selection of the collateral channels are crucial factors for the success of the procedure. Septal collaterals are safer and should be the first choice whenever possible. On the other hand, epicardial collateral channels can be used with a high rate of success and low incidence of procedural complications when revascularization procedures of CTO lesions are performed by experienced interventional cardiologists in high volume laboratories.

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KAKO BEZBEDNO IZVESTI REKANALIZACIJU HRONIČNE TOTALNE OKLUZIJE RETROGRADNIM PRISTUPOM

Nenad Božinović[1,2], Zoran Perišić[1,2], Tomislav Kostić[1,2], Bojan Maričić[1], Sonja Šalinger[1,2], Milan Živković[1], Ines Veselinović[3], Tijana Maričić[3], Svetlana Apostolović[1,2], Jelena Perišić[1]

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Hronična totalna okluzija (engl. *chronic total occlusion* – CTO) koronarne arterije definiše se kao totalna (100%) opstrukcija anterogradnog protoka u nativnoj koronarnoj arteriji stara više od tri meseca.

Podaci pokazuju da se od 7% do 15% CTO leči perkutanom koronarnom intervencijom i da rekanalizacija CTO i dalje predstavlja vrhunac u perkutanim koronarnim intervencijama. U literaturi su opisane tri različite tehnike za CTO rekanalizaciju: antegradna eskalacija žice, anterogradna disekciona tehnika i retrogradna disekciona tehnika. Septalne kolaterale i dalje predstavljaju najčešći izbor u velikom broju retrogradnih CTO intervencija zbog najniže stope ozbiljnih komplikacija. Perforacije septalne kolaterale uglavnom nisu praćene ozbiljnim komplikacijama i obično se spontano povlače. Sa druge strane, korišćenje epikardnih kolaterala može biti praćeno velikom stopom uspeha i malom incidencijom proceduralnih komplikacija kada procedure revaskularizacije CTO lezija izvode iskusni interventni kardiolozi.

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***Ključne reči**: hronična totalna okluzija, perkutane koronarne intervencije, kolateralni krvni sud*

Case report

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A CASE OF SIGMOID COLON CANCER PROLAPSE AS A RARE CAUSE OF ADULT ISCHEMIC INTUSSUSCEPTION

Lidija Djordjević[1,2], Toplica Bojić[2], Mirjana Marinković[1,2]

Intussusception in adults is present with nonspecific symptoms, which can present diagnosis challenges. Herein, we describe a case with extremely painful sensitivity in anal prolapse of soft-tissue mass with hematoma, as well as signs of ischemia. An operation was performed, during which a large sigmoid intussusception with a 7-cm ulcerative tumor, being the leading point, was found. While the prolapsed intussusception per anus is most commonly associated with the rectum, the possibility of a sigmoid colonic prolapse should always be considered. In adults, intussusception of the large intestine is very often associated with colon cancer, and for this reason, it is necessary to undergo a surgical procedure in such patients.

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Key words: *diagnosis, intussusception, sigmoid prolapse, treatment*

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Introduction

Intussusception occurs most often in children, and this condition is very rare in adults. Bowel obstruction caused by intussusception occurs in 1% to 5% of cases (1). The prolapse of an intussuscepted "lead point", such as lipoma or tumor, is rare. Intussusception of the sigmoid colon, which clinically mimics prolapse of the rectum, occurs very rarely in adults (2). We present a complete prolapse of the rectum and sigmoid colon caused by adenocarcinoma located on the sigmoid colon.

Case presentation

A thirty-three-year-old female patient was admitted as an emergency with anal prolapse after defecation. The patient complained of severe pain in the anal area and the presence of dark red blood that came out of atypical 20 × 7 × 5 cm prolapsing soft tissue mass. Clinical examination showed extremely painful sensitivity in prolapse of soft tissue mass with hematoma and signs of ischemia. (Figure 1). Opioid analgesics were used for pain treatment. The patient was clinically stable on admission (temperature 37.1 °C, heart rate 92 bpm, blood pressure 140/85 mm Hg). A physical examination showed that her abdomen was soft with tenderness at the lower part of the abdomen, with no rebound tenderness. The patient was treated by general practitioners for several years with the diagnosis of bleeding hemorrhoids. The colonoscopy was never performed. Further, the patient had laboratory signs of sideropian anemia. An examination under anesthesia was performed, during which the ulcerative tumor was verified on the prolapsing soft tissue mass. The mass was reduced successfully.

The patient underwent emergency surgical intervention when part of the sigmoid colon was verified with hematomas and ischemia (Figure 2). Hartmann's procedure was performed due to dilated and unprepared colon. After the surgery, a resected sigmoid colon was opened, when the 7-cm ulcerative tumor was verified (Figure 3). The patient had an uneventful postoperative course. The final diagnosis was of the sigmoid colon adenocarcinoma causing intussusception and the tumor prolapsed out through the anus.

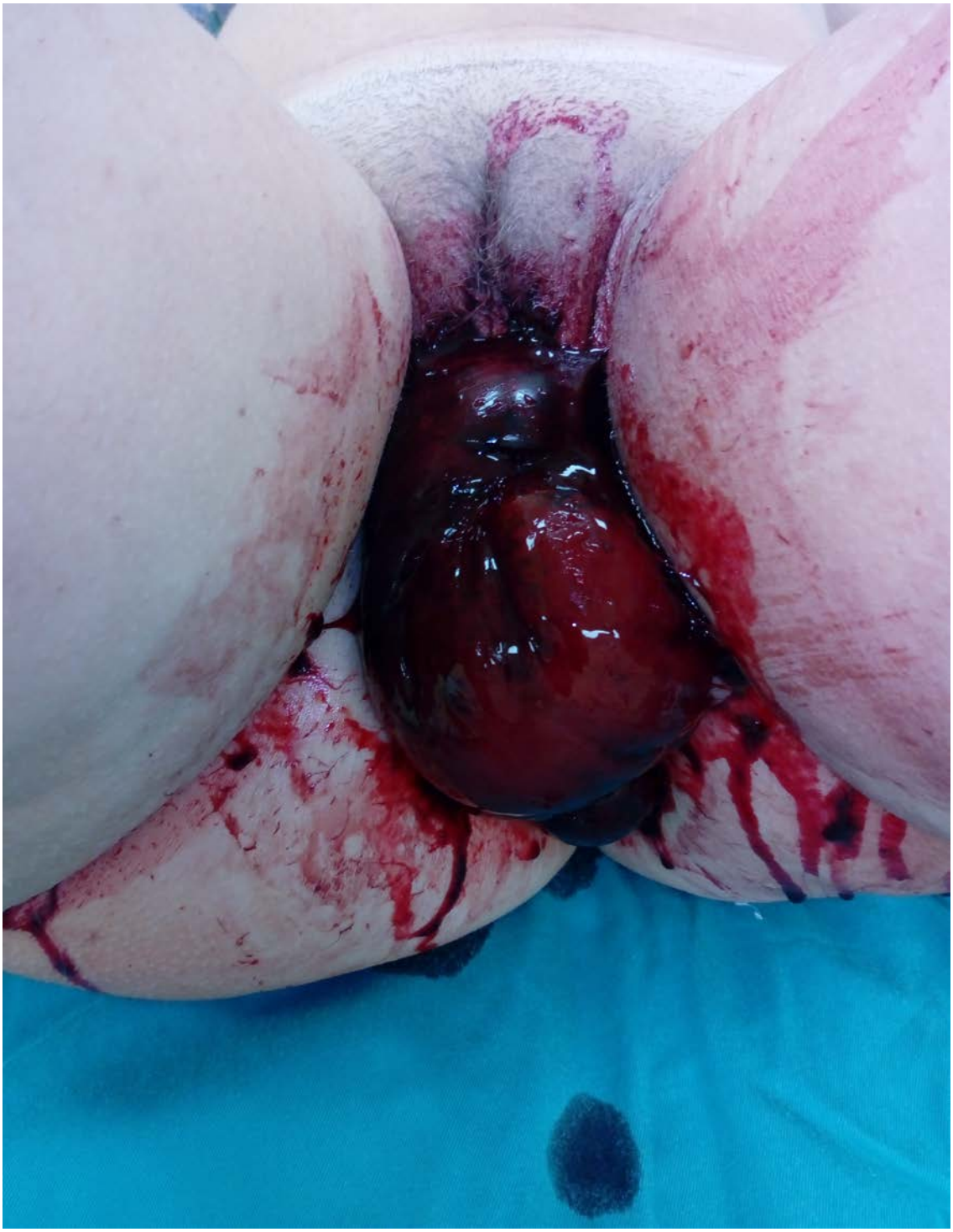

Figure 1. The prolapsed sigmoid colon portion from the anus

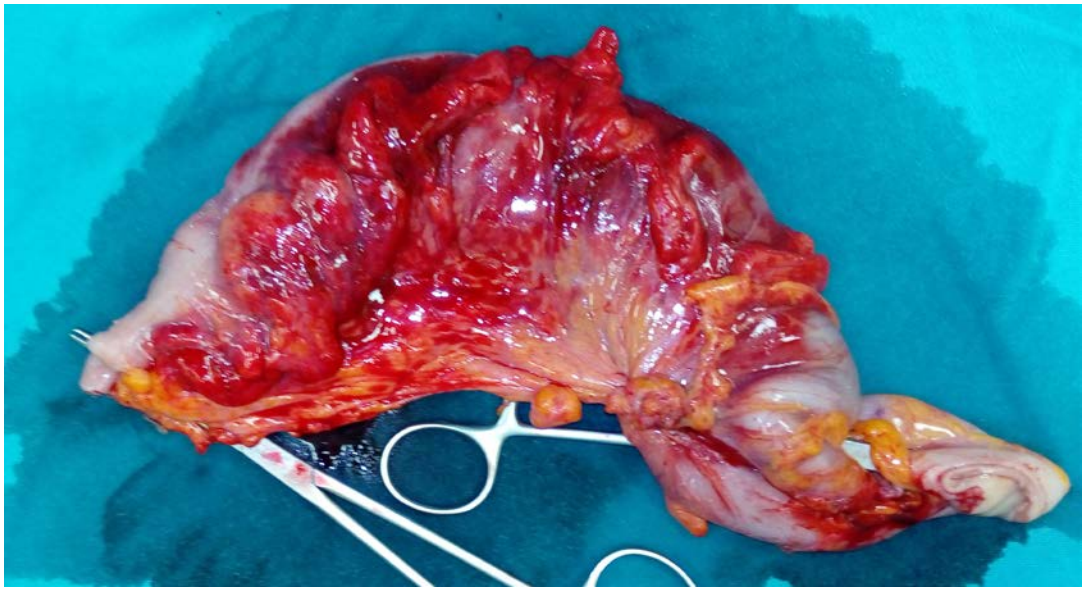

Figure 2. Sigmoid colon with the presence of haematomas and ischemia

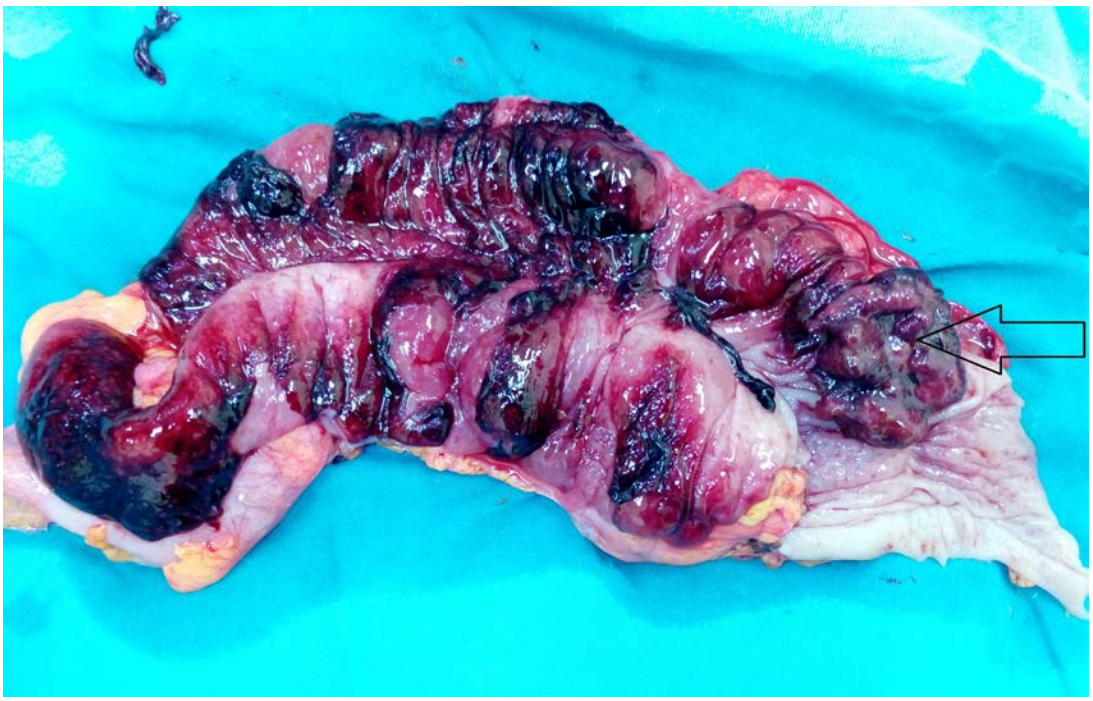

Figure 3. Resected sigmoid colon with ulcerative tumor

Discussion

Clinical manifestation of intussusception in the adult population is very rare. Ileus caused by intussusception occurs in about 1% of cases, and the cause is hospitalization in about 1% of patients (3). The clinical triad of symptoms: abdominal pain, mass and per rectal bleeding is characteristic of the children's population, while adult patients do not necessarily have all these symptoms. A study by Wang et al. (4) showed that this triad of clinical symptoms can be found in 9.8% of adult patients. It is necessary to point out that, in children, in about 70% of cases intussusceptions are idiopathic. However, in adults, the most frequent cause of intussusception is tumor. A malignant tumor is the most common cause of anal prolapse of the colon (5).

Prolapse of the rectum caused by a malignant tumor is very rare, and so far it has been described in the literature only in a few papers (2). Prolapse of the sigmoid colon is an

even rarer entity (6, 7). It is very important to point out that when performing a clinical examination we should, if possible, verify a lead point lesion on the protruding mass because this cannot be verified when rectal prolapse occurs (8). This situation was also present in our patient, where there was a 7 cm ulcerative tumor serving as an intussusceptum at the sigmoid colon, leading to prolapse through the anus. Prolapsing intussusception has a very non-specific clinical picture, and it is very easy to make a mistake in establishing a diagnosis and suspect rectal prolapse. This is a characteristic of the initial stage of the disease when the symptoms of sigmoid colon obstruction are not fully displayed. For this reason, exercising caution in setting the correct diagnosis is of critical importance, especially given that such a condition can stand pre-malignant or malignant sigmoid colon lesion(s). In this specific case, the additional problem was caused by the venous blood stasis with very pronounced hematomas and ischemia, which additionally made intussusceptum particularly challenging to diagnose. Symptoms of ischemia require a rapid response by the surgeon. Based on the literary data, the initial recommended therapeutic measure is the reduction, unless there is a doubt of malignancy (9). Studies have shown that 60% of colonic intussusceptions are caused by malignant tumors (5, 9). For this reason, the use of preoperative colonoscopy or colonoscopy during surgery is recommended to avoid unnecessary resections of the colon and rectum in the case of the presence of benign lesions (10).

In our patient, the Hartmann procedure was performed, because the colon was not prepared, and there was marked dilatation and swelling of the colon. An anastomosis was not performed in the patient for the aforementioned reasons, in order to avoid a high risk for dehiscence of the anastomosis. The clinical practice of our hospital is to give priority to staged surgery in patients with obstructive carcinoma of the left colon.

In establishing the diagnosis of intussusception, the use of colonoscopy and MSCT of the abdomen and pelvis has a very important role. Colonoscopy, as a diagnostic procedure, should clarify the cause of intussusception and provide a histological sample of the tumor. In this way, further treatment will be planned. Intussusception can be most accurately diagnosed with the help of MSCT of the abdomen and pelvis. With the help of this diagnostic method, the place of intussusception, extent, basic lesion, dilatation of the intestine and signs of obstruction can be determined. It should be emphasized that MSCT is a noninvasive diagnostic method (8). Unfortunately, in this case, MSCT of the abdomen and pelvis was not performed for technical reasons, which ultimately did not affect the course and outcome of the treatment, although the authors consider that this diagnostic procedure should have a primary role in an adequate diagnosis setting. After the tumor visualization in general anesthesia, the colonoscopy did not make sense, as it would have postponed urgent surgical intervention and exacerbated the sigmoid colonic ischemia.

In conclusion, the prolapsed intussusception per anus is most commonly associated with the rectum, but the possibility of a sigmoid colonic prolapse should always be considered. If the diagnosis of intussusception of the colon in adults is made and it is caused by a malignant tumor, it is necessary to perform a surgical intervention to obtain an adequate diagnosis and provide adequate treatment.

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SLUČAJ PROLAPSA KARCINOMA SIGMOIDNOG KOLONA KAO REDAK UZROK ISHEMIJSKE INTUSUSCEPCIJE KOD ODRASLIH

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Intususcepcija je kod odraslih prisutna sa nespecifičnim simptomima, te može biti veoma izazovna kada je reč o postavljanju dijagnoze. Opisan je slučaj izrazito bolnog analnog prolapsa mekotkivne mase sa hematomom i znacima ishemije. Urađena je operacija i pritom je pronađena velika sigmoidna intususcepcija sa ulceroznim tumorom na 7 cm od anokutane linije. Prolbirana intususcepcija kroz anus najčešće je rektalnog porekla, mada uvek treba uzeti u obzir mogućnost prolapsa i sigmoidnog kolona. Intususcepcija debelog creva je kod odraslih često povezana sa malignitetom debelog creva, pa zahteva laparotomiju za dijagnozu i terapiju.

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***Ključne reči**: dijagnoza, intususcepcija, sigmoidni prolaps, lečenje*

Case report **UDC: 616.895-053.6**
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PSYCHOSIS RISK ASSESSMENT FOR ADOLESCENTS IN CLINICAL PRACTICE

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The importance of Ultra High Risk (UHR) state for psychosis has been increasingly acknowledged to such an extent that Attenuated Psychosis Syndrome (APS) is being considered as a new diagnostic category in the DSM-5. The suggested criteria for attenuated psychosis syndrome presuppose the presence of at least one of three attenuated positive psychotic symptoms (disorganized speech, delusions and/or hallucinations) with a frequency of at least once weekly in the past month. These symptoms would exacerbate in the past year, cause disability, distress or help-seeking behavior, and could not be explained by another mental disorder.

The paper aimed to present the assessment of attenuated psychosis syndrome in a male adolescent aged 17 and its implications in diagnosis and management. Apart from clinical examination, the assessment was performed using the Comprehensive Assessment of At-Risk Mental States (CAARMS version 2006) and the Social and Occupational Functioning Assessment Scale (SOFAS).

Structured assessment of Attenuated Psychosis Syndrome, especially in adolescence, represents a delicate task for mental health professionals. It gives an opportunity to identify high-risk individuals for psychosis, provide early intervention targeting the present symptoms, reduce stress, improve functioning and at least delay the progression to the clinical picture of full-blown psychosis.

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Key words: *psychosis risk, adolescence, attenuated psychosis syndrome, assessment*

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Introduction

Being able to identify and intervene at early stages in the course of psychosis has brought about "close-in" methods for identifying young people with an at-risk mental state for psychosis. The concept “At Risk Mental State” (ARMS) is described as “a state that indicates a high but not imminent risk of developing psychotic disorder in the near future” (1). Individuals in the ARMS can be more precisely defined as being at Ultra High Risk (UHR) state for psychosis (2) with a specific set of criteria known as the Ultra High Risk criteria (UHR criteria). According to Yung et al. (3) UHR criteria involve young individuals, between 14 and 30 years old, reported to meet one of the following criteria—experiencing attenuated positive symptoms during the past year; experiencing Brief Limited Intermittent Psychotic Symptoms (BLIPS) lasting no longer than 1 week and abating spontaneously; or presence of a genetic risk factor (family history of psychosis; schizotypal personality disorder of the individual) in combination with a recent significant drop in psychosocial functioning (GRFD) during the previous year. In general, individuals who present any of these three risk conditions are at risk of developing a psychotic disorder.

The conversion rate in UHR samples to first-episode psychosis, mainly of the schizophrenia spectrum, regardless of applied UHR criteria, was estimated to run from 18% at 6 months, 22% at 12 months, 29% at 2 years, to 36% at 3 years, no matter what psychometric instruments are used (4). About 60% of UHR individuals who do not develop psychosis continue to exhibit subthreshold psychotic symptoms or meet criteria for other mental health disorders (5) with social functioning impairments as common as in other mental disorders (6). Poor social functioning and a drop in social functioning as well as poor cognition have been shown to be predictors of transition to psychosis together with some environmental fac-

tors, primarily trauma, bullying, and cannabis abuse (7 – 9). The conversion rate of psychosis in adolescents is lower and the risk for psychosis is 10.4% at 6 months, 20% at 12 months and 23% at 24 months (10).

The importance of the UHR stage for psychosis has been acknowledged to such an extent that an Attenuated Psychosis Syndrome (APS) is being admitted as a new diagnostic category in the DSM-5 (11). APS and its diagnostic structure reside primarily on the risk criteria from the Structured Interview for Psychosis Risk Syndromes, SIPS (12) and the Comprehensive Assessment of At-Risk Mental States, CAARMS (3) which relate to subthreshold psychotic symptoms and the prodromal states of schizophrenia. The proposed criteria for APS involve the presence of at least one of three attenuated positive psychotic symptoms (disorganized speech, delusions and/or hallucinations), occurring at least once a week in the last month. Furthermore, these symptoms have aggravated in the past year, causing distress, disability, or help-seeking behavior, and are not better explained by another DSM-V disorder (11). APS features often have an onset in adolescence (13, 14) on average, at the age of 15 or 16 (11).

The aim of the paper was to present the APS assessment in a male adolescent aged 17 and to discuss its implications in diagnosis and management. The assessment was conducted at the Child and Adolescent Psychiatry Department of the Centre for Mental Health Protection, University Clinical Centre Niš. Apart from the clinical examination, the following assessments were used: The Comprehensive Assessment of At risk Mental State (the CAARMS 2006 version) and The social and Occupational Functioning Assessment Scale (SOFAS). CAARMS is a semistructured interview designed to assess ultra-high-risk criteria for psychosis and a range of other psychopathological conditions considered to suggest the imminent development of a first-episode psychotic disorder (3). There are seven CAARMS subscales that include: positive symptoms (unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech), cognitive change attention/concentration, emotional disturbances, negative symptoms, behavioural change, motor/ physical changes and general psychopathology. This four positive symptoms are used for the assessment of APS and BLIPS. The intensity and frequency of symptoms are scored on a 7-point Likert scale (ranging from 0 to 6), and distress caused by the symptom is scored on a 0-100 scale. The CAARMS separates three subgroups of patients with an ARMS for psychosis 1) vulnerability group, 2) group 2a—APS (subthreshold intensity) and group 2b—APS (subthreshold frequency) and 3) BLIPS. The CAARMS is designed for repeated use over time, for example monthly to six-monthly.

To assess the drop in global patients functioning we used the Social and occupational functioning assessment scale (SOFAS).

Case presentation

We presented a case of 17-year-old NN male attending the third, final year of vocational chemistry high school, living with his parents in an urban environment. He said at the time of his interview that he visited a psychiatrist for the first time and that he would have come earlier “to require help”, but his movement and contact with health services were limited because of the COVID-19 Pandemic. His parents stated that the adolescent had exhibited changes in behavior in the previous year but those changes were tolerated and considered to be a consequence of growing up and puberty. The mother said that the adolescent had occasionally complained of hearing voices but she thought that he was dreaming them. The adolescent claimed to have been feeling tense, empty and languorous for a prolonged period of time (over 6 months). He did not complete his school duties regularly and he would often skip school. He was "under very high pressure" at school and had “unusual experiences” there. Multiple times a week during school time, he was afraid that his classmates controlled his thoughts, but wondered if they could do it and if they could know his thoughts. That experience, he stated, had caused severe anxiety. He often believed to be the center of their interest, he was suspicious of their intentions and occasionally thought they were fixing him bad grades. Being in their company provoked tension, impending danger and increased anxiety. He neglected school material, but he was interested in and read philosophical works and topics related to the occult. He revealed that he had had a serious alcohol intoxication a few months before, which required a one-day hospital treatment. He stated that he had occasionally used alcohol with alprazolam "to calm down". He had previous experience with occasional cannabis abuse, but stated that he had not used it in the previous six months. He often engaged in self-harm, he cut himself with a razor and put out cigarettes on his arms to relieve tension, but as he stated, “self-harm does not bring me relief as before”. He heard voices that were getting more intense in the last two months, usually in the evening, before going to bed, and intermittently—at times almost daily, and at other times he did not hear them at all. The voices he heard were male, and came from the outside as if someone was saying them in his ear, sometimes there was one, sometimes more; the voices repeated his thoughts "to hurt someone mentally or physically" or repeated parts of the conversation he had during the day. He believed that everyone had voices like the ones he heard, but he got used to them, did not fear them, but was afraid that he might obey them. He also stated that he had been struggling with them

more and more and that he believed that there was a high probability of acting upon them. The adolescent reported having had difficulties to fall asleep, it took him more than an hour to fall asleep and he woke up early in the morning (around 3 – 4 am), not being able to fall asleep until he went to school. He had nightmares, but he did not want to talk about their content because they were filled with aggression. He was feeling indisposed, irritable, easily aggravated and angry lately, which was why he came into conflict with the people around him. During the first term at school, his conduct grade was reduced and he was reprimanded by the school principal. He admitted having had suicidal thoughts and considered ways to commit suicide, but still had no definite plan.

Personal history showed that he was the only child of his parents, without any significant behavioral and emotional problems in his early life years. The family denied the existence of any previous stress situations in the family or at school. There were difficulties adapting to peer groups during growing up. Family history showed no records of psychiatric heredity.

Discussion

Diagnostic and clinical assessment of individuals with suspected UHR state for psychosis often requires extensive backing information to distinguish the often nuanced symptoms in the prodromal period and differentiate not only psychosis from prodrome but also prodrome from normal adolescent behavior (15). The psychopathology described in the aforementioned presentation fulfils the criteria for APS. Considering the CAARMS criteria subscales, the psychopathology meets score 4 (moderately severe) on unusual thought content due to the fact that he has ideas that other people have particular and unusual significance and feels that his experiences may be coming from outside. There is a score 3 on the frequency and duration scale as the psychopathological symptoms occur 3 to 6 times a week—less than one hour per episode. Non-bizarre ideas that included increased self-consciousness and suspiciousness were present as moderate (score 3) and their frequency and duration were twice a week over one hour per occasion. On the perceptual abnormalities scale, the symptoms were rated with a 4 (moderately severe) as attenuated range, given that the adolescent confirmed auditory changes and was able to give plausible explanations for these experiences. The frequency and duration were rated as 3 due to the fact that symptoms occur 3 to 6 times a week and last less than one hour per occasion. It was estimated that the above mentioned positive symptoms had no relation to substance abuse and the level of distress was nearly 80% in relation to symptoms. There was no evidence of disorganization of thoughts. Although the process was coherent throughout the interview, the assessed adolescent was engaged and was able to answer questions and recall his past without difficulties. He maintained good eye contact.

Given that psychopathology symptoms started within the past year, occurred at least once a month to twice a week and lasted over one hour per occasion or at least 3 to 6 times a week and lasted less than one hour per occasion, caused distress and were irrespective of relation to substance abuse or another mental disorder, these symptoms qualify for an APS. More precisely, these symptoms qualify as—attenuated psychosis group 2a/subthreshold intensity. Subthreshold intensity is defined over Global Rating Scale Score of 3 – 5 on Unusual Thought Content Subscale, 3 – 5 on Non-Bizarre Ideas Subscale, 3 – 4 on Perceptual Abnormalities Subscale or 4 – 5 on Disorganized Speech Subscale plus Frequency Scale Score of 3 – 6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities or Disorganised Speech for at least a week. Considering the patient's social and occupational functioning due to these mental health problems, we calculated a 30% drop in SOFAS score from premorbid level, sustained for a month within the past year (in the past year his highest score was 80 and the current was estimated at 50).

APS in adolescence is associated with a high level of internalizing symptoms, bullying, substance abuse, and comorbid mental disorders (6, 16, 17). In this case, the adolescent showed self-harm behavior and suicidal ideation. Literature notes that adolescents with APS have a high prevalence of self-harm behavior and suicidal ideation (65.70%), as well as a significantly higher incidence of suicide attempts (18.5%) compared to adolescents with psychosis (18). High prevalence of suicidal ideation and risk of self-harm are similar among adolescents and adults with APS (19). High suicidality may precede the first psychotic episode in both groups (19). The profile and presentation of negative symptomatology (e.g. social withdrawal) in adolescents, aged 13 to 18, with APS is similar to that in young people with a first psychotic episode (18). Children and adolescents with APS show a significant prevalence of negative symptoms combined with significant functional impairment, as it is in adults (19).

Studies examining the treatment for individuals at UHR state, including both UHR individuals and first episode psychosis, show that treatment modalities vary significantly and include cognitive remediation, family interventions, cognitive behavior therapy (CBT), integrative psychological therapy, antipsychotics, omega-3 fatty acids, glycine and d-serine, as well as combinations of these interventions (20). Treatments target existing symptoms, improve functioning, reduce stress and regulate potentially emerging diseases. There is a lot of evidence that places CBT as the most successful treatment of UHR individuals (21, 22). EPA also recommends CBT as the first-choice therapy in adult clinical high-risk patients. In cases where psychological interventions are insufficient, these are combined with a low-dose second-generation antipsychotic to manage symptoms and prevent first-episode psychosis (FEP) (23).

Conclusion

Psychosis risk assessment using both clinical experience and screening instruments can be challenging for mental health professionals. This is especially relevant for adolescence, when changes in emotional well-being and functioning are frequent and when nuanced symptoms in the prodromal period need to be differentiated not only from mental disorders but also from normal adolescent behavior. The CAARMS relies on the frequency of psychopathological symptoms, recent onset or worsening as well as distress or impairment to differentiate threshold-attenuated psychotic symptoms from typical and subthreshold experiences. It is important to note that psychosis risk assessment does not end with the completion of CAARMS or other screening instruments. Monitoring the psychopathology symptoms and the development of the clinical manifestation, comorbid disorders, and the effects of social-risk factors in all developmental stages of UHR individuals allows timely interventions that could delay, improve or even prevent the progression to a fully manifested psychotic disorder.

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PROCENA RIZIKA ZA POJAVU PSIHOZE KOD ADOLESCENATA U KLINIČKOJ PRAKSI

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Važnost stanja povišenog rizika (engl. *Ultra Hight Risk* – UHR) za pojavu psihoze prepoznata je do te mere da se sindrom atenuisane psihoze smatra novom dijagnostičkom kategorijom u DSM-5 klasifikaciji. Predloženi kriterijumi za sindrom atenuisane psihoze zahtevaju prisustvo najmanje jednog od triju pozitivnih psihotičnih simptoma (sumanutosti, halucinacije, dezorganizovanog govora) u oslabljenom obliku, ispoljenog najmanje jednom nedeljno u poslednjih mesec dana. Da bi se govorilo o sindromu atenuisane psihoze, potrebno je da je u poslednjih godinu dana došlo do pojave ili pogoršanja simptoma i da simptomi uzrokuju uznemirenost i onesposobljenost osobe koja ih doživljava, kao i traženje pomoći. Jedan od uslova za postavljanje ove dijagnoze jeste i nemogućnost boljeg objašnjenja navedenih simptoma nekim drugim (DSM-5) mentalnim poremećajem.

U radu je prikazana strukturirana procena sindroma atenuisane psihoze kod sedamnaestogodišnjeg adolescenta i diskutovano je o njenim implikacijama u dijagnostici i tretmanu. Za procenu su, pored kliničkog pregleda, korišćene Sveobuhvatna procena rizičnog mentalnog stanja (engl. *The Comprehensive Assessment of At-risk Mental States* – CAARMS, version 2006) i Skala procene društvenog i profesionalnog funkcionisanja (engl. *The Social and Occupational Functioning Assessment Scale* – SOFAS).

Procena sindroma atenuisane psihoze, posebno u adolescenciji, delikatan je zadatak za stručnjake za mentalno zdravlje. Značajno je da ona daje mogućnost da se identifikuju visokorizične osobe, da se rano interveniše ciljanjem prisutnih simptoma, da se smanji stres, da se poboljša funkcionisanje i spreči ili makar uspori progresija psihotičnih simptoma do jasno ispoljene kliničke slike psihoze.

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***Ključne reči**: rizik za pojavu psihoze, adolescencija, sindrom atenuisane psihoze, procena*

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THE EFFECT OF COVID-19 CRISIS ON CHRONIC DISEASE TRACKING: BRIDGING A DATA GAP

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COVID-19 negatively shifted chronic disease tracking and general data collection in primary healthcare facilities. The focus was moved to support the counter-pandemic efforts, while the number of registered general examinations and those dedicated to chronic diseases dropped.

In that light, the results of the algorithms dedicated to helping identify potential new chronic patients become less relevant. With a lower number of registered visits, the results of the estimate become less relevant with the increased number of unidentified patients with chronic medical cases. This research aims to improve the existing data summarization methods and increase their relevance by adding new criteria, using the potential to integrate with other medical information systems, and making them more configurable up to the patient level.

The updated data aggregation tools are evaluated against results collected in Niš Primary and Ambulatory Care Center and compared with the results from the initial version of the algorithm.

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Key words: *medical information system, history of disease summarization, chronic disease management, data gap identification*

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Introduction

Chronic medical conditions such ashigh blood pressure and diabetes hit a significant percentage of the population worldwide. In European countries, the percentage of registered patients suffering from chronic hypertension is between 30% and 45% (1, 2). Unfortunately, the Republic of Serbia is in the top 10 countries with an estimated prevalence of hypertension of one-half in the adult population (3). In many cases, the chronic disease is not discovered early enough, leading to the significant deterioration of the health status of the affected individuals (4). For this reason, any improvement in the detection of chronic diseases is of immense importance for the public health system as a whole (5). We identified this problem during the pandemic and our first result ofthe identified gap was presented in the study by Rajković P. et al.(6). From the thematic point of view, this paper represents the follow-up of the mentioned research and shows the latest results and recommendations in our research, which should bring more effective data summarization processes and routines that would help identify patients with chronic diseases.

This situation has beena well-known fact for decades, but with the COVID-19 pandemic outbreak, it worsened (7). Since, during that period, most of the medical workforce was engaged in COVID-19 units, the positions in general and specialist care became understaffed. The series of lockdowns reduced the general population's mobility which reflected in the reduction in the number of registered visits with general practitioners (GP) and specialist doctors (8).

Besides the usage of Medical Information Systems (MIS) during the pandemic period in GP and specialist units dropped in terms of quantity, the quality of collected data remains. This means the identification of the early warning signs of chronic disease, especially hypertension and diabetes (9, 10), remains possible. The early warning signs for the chronic disease could be various medical record items associated with it—like diagnosis on some examination, prescription of the specific medication, treatment, change in patient's data, etc.

Our research group has worked on developing MIS for primary care, named Medis.NET, and supplementary software tools since 2009. The installation base consists of 25

installations in the region of Southern and Eastern Serbia (11) covering a population of approximately 1.5 million and supporting both general practitioners and specialist services (12–14). Recognizing the potential to extend the basic MIS with the data analytic features we introduced an extension that provided a Data Summarization Method (DSM), integrated into an auxiliary tool. Its main aim was to detect potential patients with chronic diseases on the base of registered medical services and prescribed medications (15).

The structure of the base MIS and the mentioned extension is shown in Figure 1. The effect of the proposed methods was published by Aleksić D.et al.(15) and the designed algorithm was based on data collected between the years 2012 and 2015. The approach was proven effective in the coming years. The results for the years 2016 to 2019 were within the expected boundaries.

The transition to the updated version of DSM tool would be necessary since the structure of the collected data as well as collection methods gets changed. The COVID-19 pandemic influenced the habits of software users, and the integration services extended the software landscape. Speaking about changed user habits, our MIS has a reduced set of directly registered data, as the result of the focus shift to COVID-19-related medical services. Oppositely, the integration with the external systems brought additional data that must be treated a bit differently. The internal transition would be seamless for the end users and would come through one of the regular software releases.

The updated algorithm was tested in parallel for the period 2016-2019 with the COVID crisis from 2020 to 2021 (6). The mentioned summarization algorithm has been further extended (Figure 2), and its present form is discussed in this paper. In this paper, we wanted to compare the results we got from the two algorithms and point out the differences and improvements we implemented. Furthermore, the updated DSM offers a higher level of customization. This will give the end user better control over the identification process.

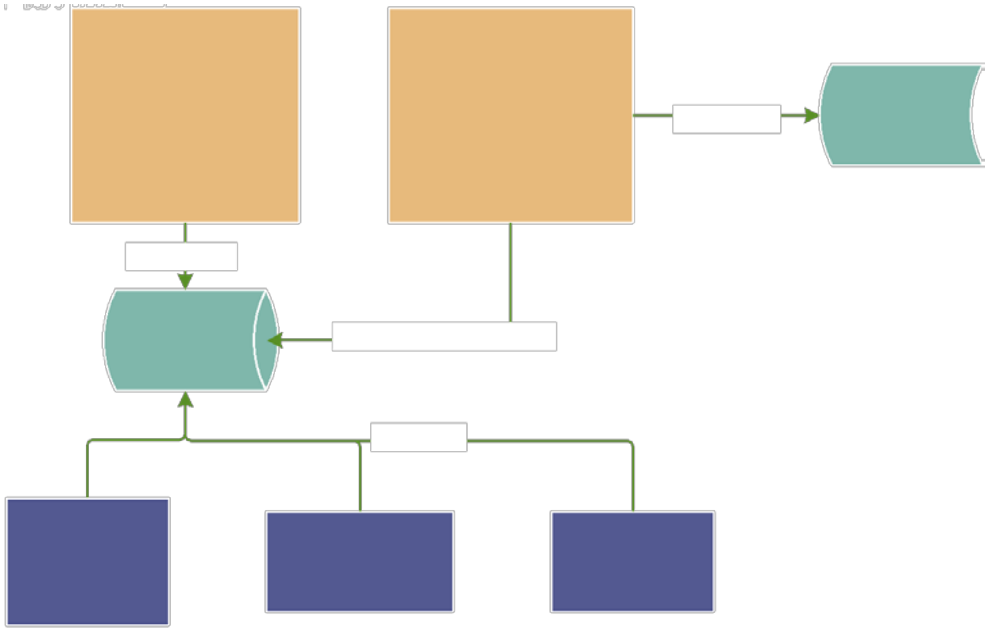

Figure 1. The extended system architecture

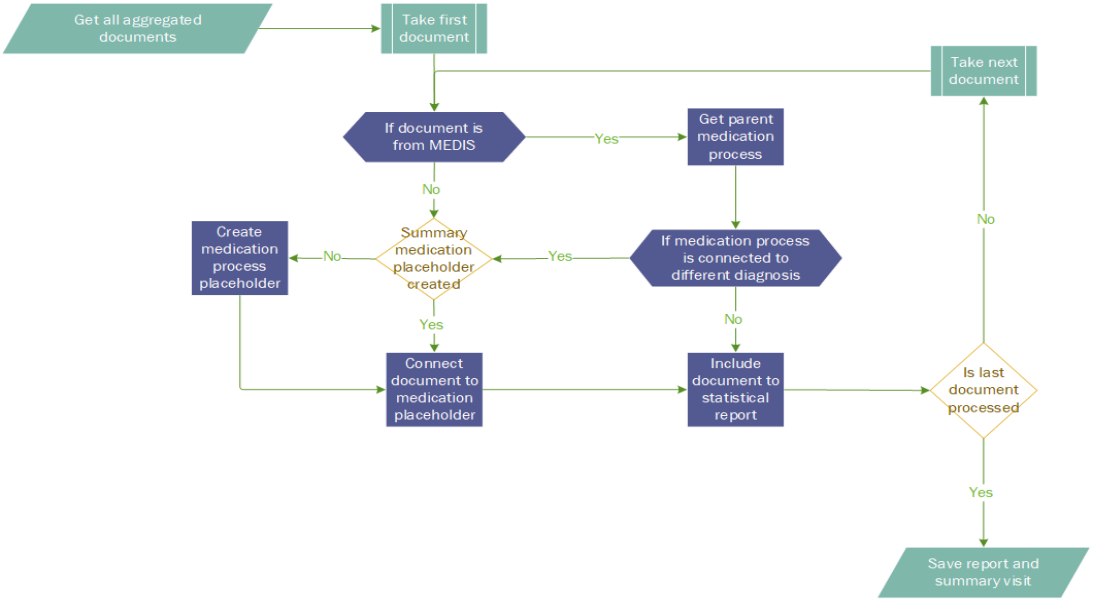

Figure 2. The adaptation of the data extraction/summarization algorithm originally presented in the study by Aleksić D. et al. (15)

Related work

The challenge started with the COVID-19 outbreak in March 2020 (16). In the following months, the reduction of registered medical care institutions dropped worldwide (17) to one quarter, and in some cases (18) even to one-tenth. Due to the reduced number of registered medical services, the number of identified patients dropped too, making the already designed and implemented algorithm less effective. To bridge the potential gap, we decided to improve our DSM, by improving its routine and by adding new identification parameters.

The studies of MIS systems used during the pandemic (19) show a dramatic activity decrease in March and April 2020. This period was then followed by a significant increase in pandemic-related activity (as added support tools emerge) which partially covered the reduction in the number of medical services related to non-COVID-19 patients.

The research by Patel S.Y. et al. discusses one different consequence of the pandemic: the growth of telemedicine (18). Analyzing data from the United States, the authors concluded a rise of close to 20% in the first half of 2020, while the number of patient visits dropped to close to one-third. Combining telemedicine with regular visits, the overall reduction in visit registration ended at 10% looking at the situation from 2020.

The overall data summarization paradigm is often extended nowadays with the analysis of different medical images presented by Wang S. et al.(20). The authors modified the existing image processing methodology, used to detect common pneumonia, by including deep learning techniques to make the algorithm that could help in early detection of COVID-19. The positive influence of such an approach to our work was the suggestion to use an adaptive estimation approach which allows the system to propose different setup parameters when number of false positives increases. Unfortunately, the downside of such approach is the high number of false positives which requires further adaptation by including images of the pathogenic negative patients in the analysis.

Cases like the COVID-19 pandemic prove that medical professionals cannot rely only on direct data collection from MIS systems, but any additional tools prove to be helpful and bring an additional level of data collection quality. The collateral benefit of all these scenarios is that they could remain active during regular and general emergencies, making the healthcare system more effective.

Aim

The main objective of our research was to improve the existing data summarization methods and increase their relevance by adding new criteria and making them more configurable. The outbreak of COVID-19 made a negative impact on medical research (21) as well as regular healthcare routines (17, 18), including chronic disease tracking (19). The entire health system switched its focus to support the counter-pandemic efforts (22). Medical personnel were reassigned from their regular duties to COVID care (23), and the potential number of medical examinations was reduced significantly. In some periods, the number of non-COVID-19-related treatments dropped to under one-third of the usual number (24).

Facing the significantly reduced data set, the data summarization systems identified fewer potential patients than expected. The immediate consequence was that the results of the algorithms dedicated to helping in the early detection of potential new chronic patients became less relevant. Since the general lifestyle during the pandemic becomes more stressful, the number of chronic patients will grow at least the same rate as during the regular situation. To overcome this problem, we launched research that should improve our data search algorithms to identify more patients who should be summoned for the control check-ups.

Material and Methods

The material used in our research was a set of data gathered by Niš Primary and Ambulatory Care Center (in Serbian *Dom zdravlja Niš*, in further text DZN) personnel from 2010 to 2022, using MIS Medis.NET. For the most accurate data analysis, we relied on DZN, our largest user with the highest number of registered patients. DZN is a public healthcare facility and the main primary medical care provider for a quarter-million-sized city and its surrounding area.

The collected data were organized and well-structured according to open EHR (25) standards. The choice of the international standard during the system design and development helped in later integration and made all the developed algorithms useful for other MIS instances based on the same set of standards. Our primary interest was focused on medical records that were connected to the most frequent chronic diseases in the area covered by DZN—namely I10 Essential (primary) hypertension, E11 Type 2 diabetes mellitus, I49 Cardiac arrhythmia, I20 Angina pectoris, and E10 Type 1 diabetes mellitus (Table 1). As it has been mentioned in the previous section, our main objective was to help in the early detection of chronic diseases based on the data collected both in DZN and external sources.

The initial methodology for the support in the detection of potential patients suffering from chronic diseases relied on the data summarization methods and tools that we proposed in our research (15). Due to the applied standards, the solution could be used for the development of the different extensions of any open EHR based MIS. For example, the approach was used for the visualization of the clinical structure document (26). Our research group continued development to support the pandemic effort (27) during 2020, but the method itself was acknowledged as part of the general clinical decision support paradigm (28).

It is important to point out that the summarization algorithms werenot intended to automatize the decision but to act as a warning and suggestion tool in cases when patients hadmany simultaneous diagnoses and frequently visited multiple medical professionals. The secondary benefit wasthe possibility to generate lists of the patients that could be summoned for the periodical preventive medical exams.

The base summarization algorithm was built on the analysis of medical documents generated within DZN for patients who have not yet been marked as ones with chronic diseases. The algorithm would analyse all the documents created within the predefined period and generate a warning to the medical practitioner if there were a number of medical documents related to a chronic diagnosis. The level of the warning depended on the number of discovered medical documents. When the doctor received the warning, he could decide whether to consider further action or discard the notification. Considered documents included all kinds of medical notes, prescriptions, treatments, or requests for further specialist examinations.

Table 1. The number of patients with the most common chronic diseases identified and officially verified in the period 2018-2022—2022 is given as an estimate followed by the value until November 30th

Diagnosis	2018	2019	2020	2021	2022
Number of newly identified patients	14127	13208	9044	9232	9246 (8476)
E10 Type 1 diabetes mellitus	515	506	337	285	272 (249)
E11 Type 2 diabetes mellitus	3433	3234	2246	2779	2970 (2723)
I10 Essential (primary) hypertension	6834	6668	4434	4315	4573 (4192)
I20 Angina pectoris	1543	1226	829	715	602 (553)
I49 Cardiac arrhythmia	1802	1577	1198	1138	829 (760)

Unfortunately, the accuracy of the suggestion tool, designed in such a way, depended mostly on the volume of the collected data. During the regular situation, when people regularly visit their GPs, the number of registered medical services and documents is stable, maintaining the required level of precision. When the pandemic started, the number of visits related to non-COVID-19 cases dropped, in some months, to one-third of the usual. The additional problem with the summarizing tool is that many patients nowadays visit multiple medical institutions, and their data are scattered across multiple databases. This problem is more notable in specialist departments than GPs since one patient usually visits one GP, but specialist examinations are requested from several specialists. This led to a data gap that could be easily identified during the simple data analysis (6). All the mentioned problems led to the requirements for the extension of the data summarization algorithms, tools, and usage approaches to reduce the identified data gap.

The first point was to make the data range between two identified occurrences of the document with the chronic diagnosis configurable. This would give us the immediate ability not to look at the few predefined periods (14, 30, and 90 days (about 3 months) as in the initial research), but to try with the extended periods, such as 120 or 180 days (about 6 months).

This proved beneficial for periods such as the spring/summer of 2020. The next update was not to include only diagnosis and the length between occurrences, but also patient demographic data such as age, living location, working location, family status, and whatever could be identified as important.

The next point was to include data from external institutions whenever possible. Developed integration services provided by the Serbian Ministry of Health allowed merging data from various sources (Figure 3). In this way, the number of checked documents grew higher giving a better success rate for the results.

Regarding usability improvements, two main points were suggested—raise the warning when the number of visits was too low according to predefined parameters and suggest the aggregated care process containing all the extracted data from various visits that gave the results with the chronic diagnosis.

The definition of the “too low” number of visits must be left to medical professionals to determine according to the patient’s demographic data, such as age and/or gender. The MIS could give the initial suggestion according to the statistics shown in Table 2, but the final decision must be in the hands of medical professionals.

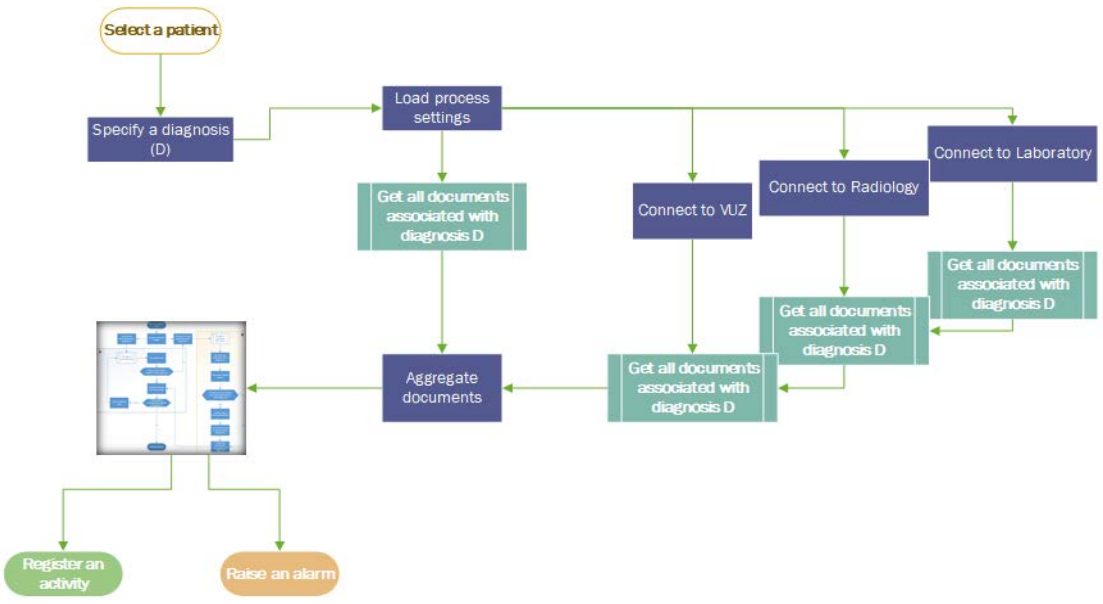

Figure 3. The extension of the identification process around the data summarization algorithm

Table 2. The number of potentially identified new patients (old method/new method) summarized for the period 2018–2022

Row Labels	Number of verified patients	Number of potential new patients (old method)	Number of potential new patients (new method)
2018	14127	2926 (20.71) %	5069 (35.88)%
E10	515	87 (16.89) %	167 (32.43) %
E11	3433	420 (12.23) %	850 (24.76) %
I10	6834	1775 (25.97) %	2717 (39.76) %
I20	1543	267 (17.3) %	640 (41.48) %
I49	1802	377 (20.92) %	695 (38.57) %
2019	13211	3438 (26.02) %	5433 (41.12) %
E10	506	127 (25.1) %	210 (41.5) %
E11	3234	527 (16.3) %	941 (29.1) %
I10	6668	2115 (31.72) %	3072 (46.07) %
I20	1226	261 (21.29) %	544 (44.37) %
I49	1577	408 (25.87) %	666 (42.23) %
2020	9044	2494 (27.58) %	3693 (40.83) %
E10	337	104 (30.86) %	167 (49.55) %
E11	2246	366 (16.3) %	644 (28.67) %
I10	4434	1531 (34.53) %	2021 (45.58) %
I20	829	175 (21.11) %	371 (44.75) %
I49	1198	318 (26.54) %	490 (40.9) %
2021	9232	3162 (34.25) %	4580 (49.61) %
E10	285	131 (45.96) %	195 (68.42) %
E11	2779	504 (18.14) %	938 (33.75) %
I10	4315	1906 (44.17) %	2444 (56.64) %
I20	715	213 (29.79) %	411 (57.48) %
I49	1138	408 (35.85) %	592 (52.02) %
2022	9246	2594 (28.06) %	3601 (38.95) %
E10	272	90 (33.09) %	128 (47.06) %
E11	2970	491 (16.53) %	847 (28.52) %
I10	4573	1591 (34.79) %	1978 (43.25) %
I20	602	188 (31.23) %	318 (52.82) %
I49	829	234 (28.23) %	330 (39.81) %
Grand Total	54860	14614 (26.64) %	22376 (40.79) %

Regarding aggregated care, it would be displayed as the existing medication process but highlighted properly. Data that already existed in Medis.NET were displayed through the standard layout, and the data retrieved from the external source would be displayed as imported using VUZ service (VUZ abbreviated from Serbian *Vertikalno Upravljanje Zdravstvom* meaning Vertical Healthcare Management) as shown in Figure 4. When the GP receives the warning, a simple click on it will include all the identified records as part of the separate medication as shown in Figure 5.

The structure of the improved algorithm is shown in Figure 2. The most notable improvement

compared with the previous version is that the algorithm is focused on documents themselves, reducing the number of data access by ignoring all the non-relevant sources. This becomes possible after adapting the overall data summarization process, which took all the documents from MEDIS.NET and external systems and combined them into a single list that becomes a single list source for the data aggregation algorithm Figure 3.

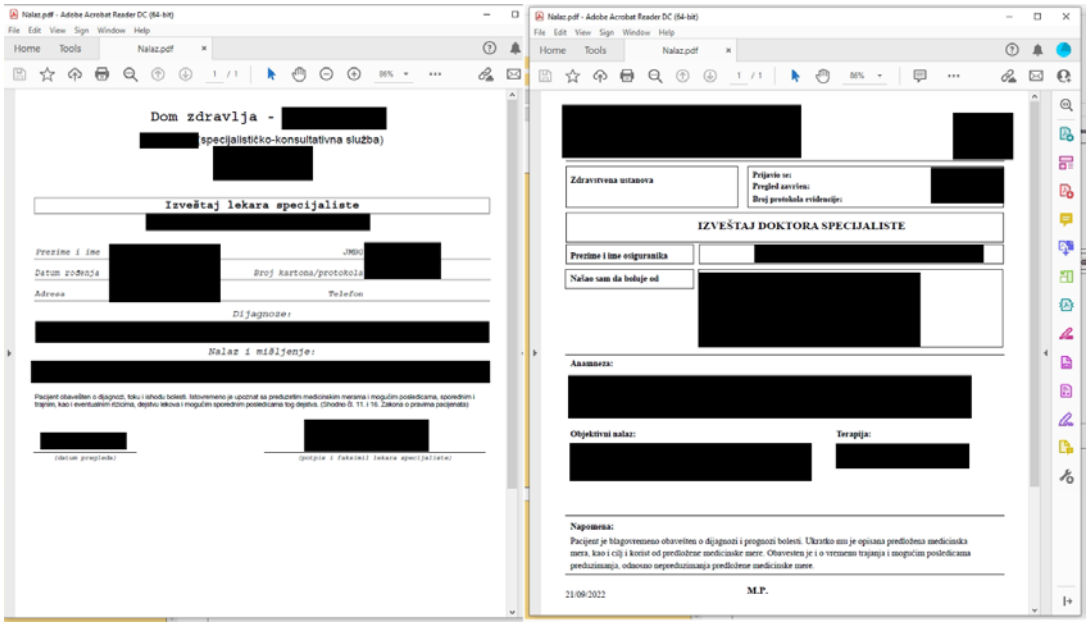

Figure 4. Examples of documents downloaded from external systems (patient-related data had to be blacked out since we could not get publication permission from the data owner until the finalization of this paper)

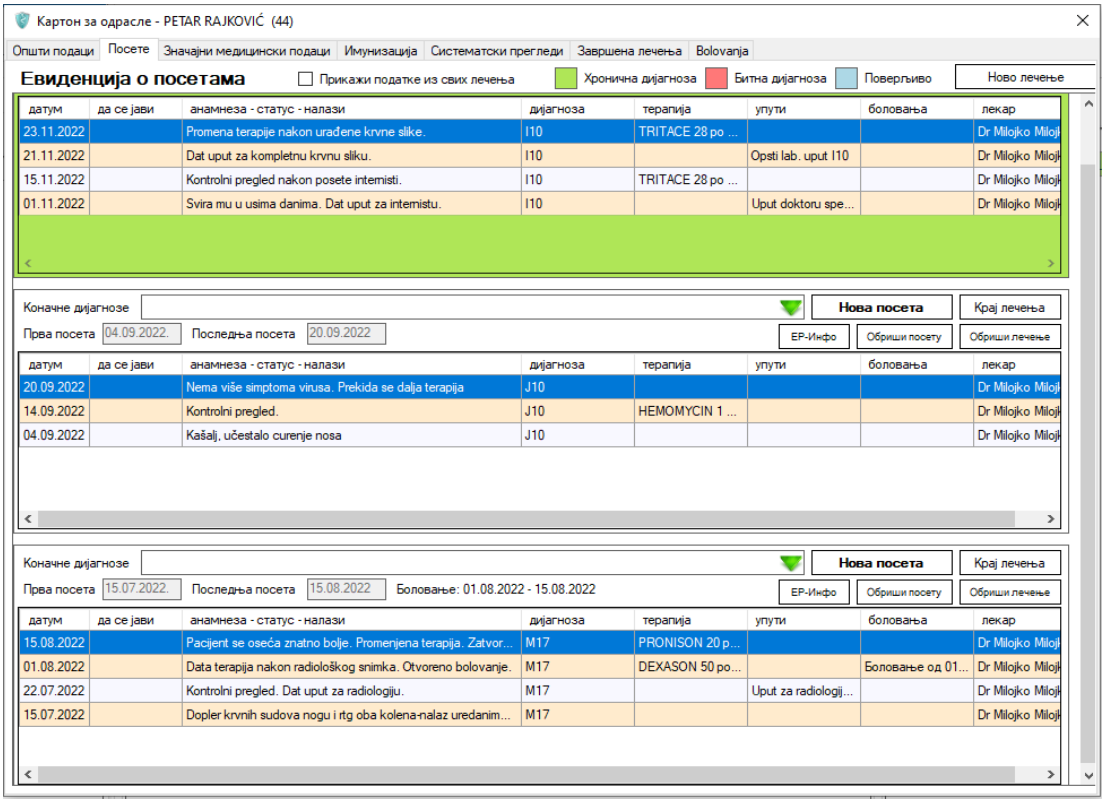

Figure 5. The example of the active medication process overview—the first medication (the one with green background) is related to the aggregated inputs for the chronic diagnoses

Results

The numbers dropped significantly in March 2020, and the situation got even worse in April. Starting from May 2020, numbers continued to recover, but except for the data collected in September (which was the month with the best epidemiological situation in Serbia in 2020) they were still under the average. In 2021, the situation tended to get normalized from April to August, but COVID-19 peaks from January and September/October reduced the total number of registered patients (Figure 6).

Checking the data in the last two years, we established that the average gap was close to 30% overall, whereas the difference in 2020 was even higher. In that situation, it was certainthat the existing data collection methods needed to be updated. Our initial approach was based on counting the number of patient visits, medical prescriptions, and specialist examinations within periods of 14, 30, and 90 days and joining the records for the selected patient by diagnosing. In addition, we provided treatment of patients with primary chronic diagnoses and secondary chronic diagnoses in separate medical services.

Joined data helped us to identify the patients and general practitioners and then decide whether to call them for the reference examinations.

With the displayed data gap, we could assume that potentially one-third of the patients could have remained unidentified. The situation was slightly better since most patients always visited the same doctor. The bottom line is that the gap was still too high to be ignored, since numerous common chronic diseases represented physical states that could deteriorate overall health status if not treated properly.

We identified the data gap and made an initial assessment using the original data summarization method (15). After including the new parameters, we reassessed the results and identified the set of parameters that brought us close to the results we had with the full data set. Recovering the number of medical examinations in the last quarter of 2021 made it possible to validate the updated method in close-to-regular conditions.

The improved method helped medical professionals to overcome the gap that was created because of the pandemic. The effect of the improved method on the reduced data set was close to the original method with a slightly higher number of false positives. Applying the updated method to situations with regular datasets increased the precision of the results.

Discussion

MIS Medis.NET started with pilot deployment in DZN in 2010. The MIS was initially installed in the GP department and later expanded to pediatrics, gynecology, laboratory, and specialist services. The system reached its full operational capability in 2012. During the system usage observations, we identified room for various improvements. One direction for such an update is the development of suggestion tools that could help medical professionals to bring important decisions.

One notable usage gap was the way in whi chchronic diseases were tracked. Besides, the GPs could mark the diagnosis as chronic; unfortunately, this feature was rarely used. The significance of such a problem becomes obvious when the patient changes the doctor. Patients are likely to miss important medical examinations or treatments during the transition as the newly chosen doctor do not have proper data upfront. Another notable case is when the patient frequently visits different doctors in different medical institutions, which could result in non-consolidated data.

The introduction of a data summarization tool was one step forward that could support users in daily activity. Using reports from our tool, we identified between 13,000 and 14,500 new potential chronic patients yearly, from 2013 to 2019. The deviation from the median number of the discovered patients was under 5%, which was the expected quality level for the results. The year 2012 was not a regular case, because that year was associated with all the patients registered since the start of the system usage. It is also important to mention that in the initial period MIS was not in use in all the departments, and only GPs actively collected data. The next important fact to point out is that in the initial period the GPs did not mark the diagnoses as chronic, despite conducting therapy and history of the disease as chronic. In later years, as the system usage became routine for all the departments in DZN, the number of potential new patients decreased to values with low variance.

For the next four years 2016–2019, the reports that came from the data summarization tool were in line with the initial findings. Unfortunately, the COVID-19 pandemic broke out in the Republic of Serbia in February/March 2020. At the end of the year, the total number of patients identified by our data summarization method dropped to slightly around one-half of the number in 2019. Periods January–March and during the summer were on the level of 2019, but during the pandemic peaks and the lockdown in April–June and in the autumn, the number was lower than one-third of the expected. The situation in 2021 was slightly better than in 2020, but the gaps created in the mentioned year still need to be overcome.

The year 2022 gave a better result and could bring the number of discovered patients closer to the pre-pandemic period, but the total number of registered patient visits was still lower than before 2020 (Figure 6 and Figure 7). There were multiple reasons for this (6). One of the problems was the constant reduction of the

number of medical professionals in DZN. The next potential reason was the change in the patient's behavior. Due to several reasons, patients chose private practice—increased number of private specialist ordinations, fear of being in the waiting room as the result of the pandemic, longer waiting time in public healthcare institutions, and increased number of patients choosing private practice as default. This analysis could lead to an interesting conclusion. However, it is outside the scope of this paper and should be considered for future research.

The proposed improvements are important in the sense that they will give an additional set of potential patients with chronic diseases compared with the original data summarization algorithm (15).

The extension of the monitoring period together with the additional demographic parameters will increase the number of identified medical documents connected with chronic diagnoses, bringing a higher number of identified patients (Figure 8). For further development of this feature, it would be necessary for it to be moved to a live environment where the doctors could use it in a real environment with the ability to provide feedback and dynamically influence the discovery rules.

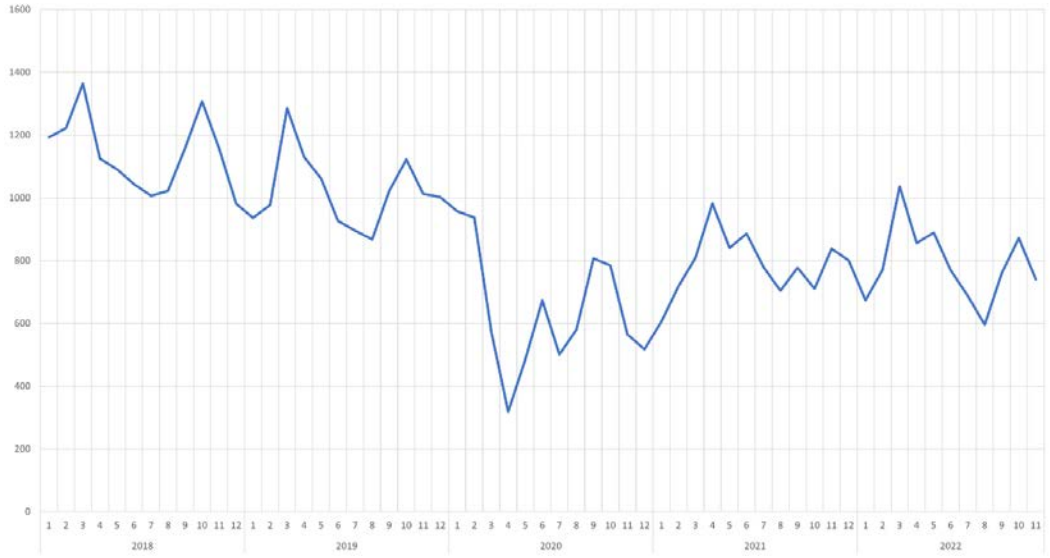

Figure 6. Total number of patients with one of the five chronic diseases per year and per month in the period January 2018–November 2022

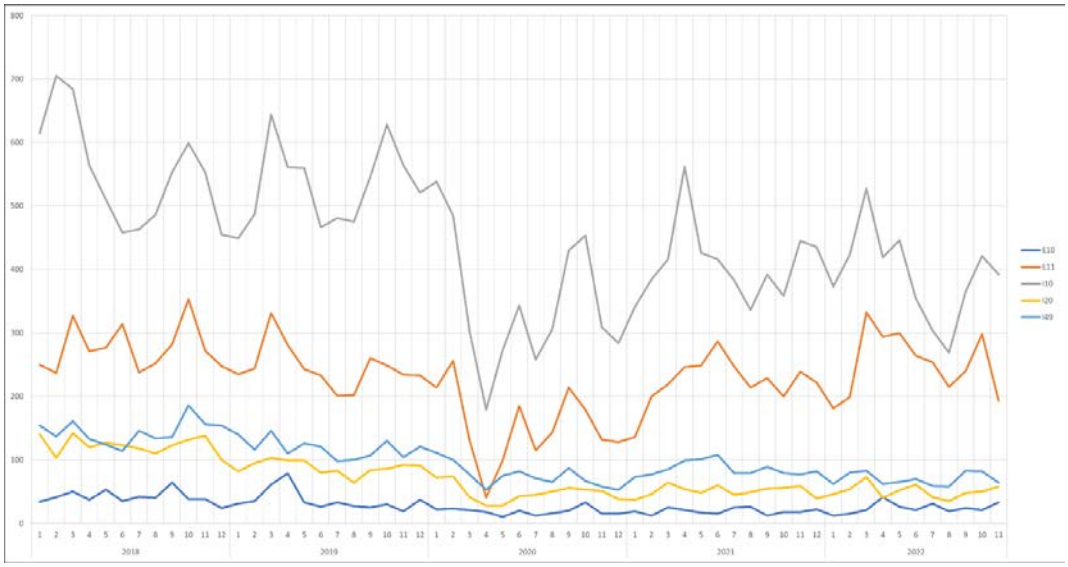

Figure 7. Number of patients with registered chronic disease (distribution per diagnosis)

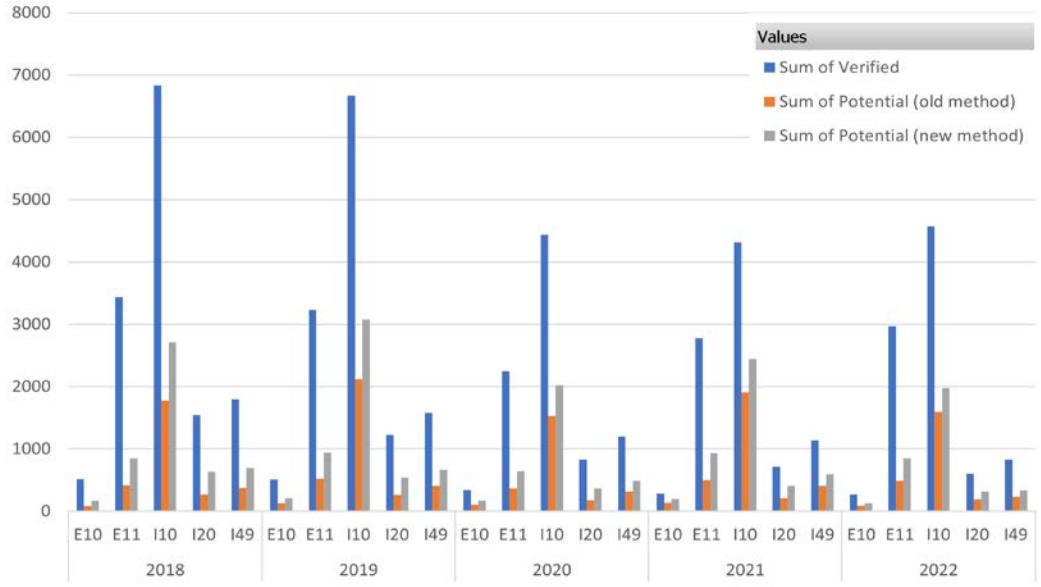

Figure 8. Comparison between the number of verified patients with chronic diseases with the number of potential patients using old and new summarization methods

The improvement in user interface should make the medical professionals work more effective. They will get the warning promptly if the patient can be marked as having chronic medical conditions. The scattered data, collected from various sources, and during a predefined period will be presented as the regular medication process, but notably marked as the data aggregation, not as the actual medication process.

All these improvements should bring new data for the integration with external medical institutions as necessary nowadays. Bidirectional communication between medical institutions is becoming a reality with the successful integration of different web services provided by the Serbian Ministry of Health. This integration will allow for the collection of scheduled patient data and display of records for specific chronic diseases from multiple sources, giving users of MIS a much better overview. The aggregated medication view will be more complete and the possibility that doctors make decisions based on the reduced data set will be lower.

With the mentioned improvements, doctors will have a powerful additional tool that could help them make better decisions for patients suffering from chronic medical conditions. This would eventually lead to more effective medical practices and improved quality of life for the patients. With further development, the doctors will be able to fine-tune their reporting services and working environment as best as possible.

Conclusion

After the change in the quantity of collected data in DZN, the existing data collection algorithm seems not to fully fit in the situation when the gap in data retrieval becomes significant. To overcome the gap, we identified a few scenarios that should be included in the filtering stage of the algorithm (Figure 2) and the preparation stage of the complete process (Figure 3). Extending the collection range will bring more people into a set of potential chronic patients. Our preliminary examination shows that if the target period gets extended to 180 days (in contrast to 90 days as we had before) it is possible to identify up to 15% more patients, with a certain number of false positives.

Many patients have started using private medical practices, and the data collected in these institutions could potentially be synchronized with data from the medical center. The problem is more administrative than technical, as the infrastructure is already implemented. Administrative decisions related to medical data sharing need to be made. Additional filtering parameters will increase the complexity of running queries, but the benefit is expected to be in the range of 10 to 15%. However, much general demographic data is missing, which makes it difficult to establish the connection between all requested data sets.

The drawback of this approach is the increased number of false positives, but it is better to call more people for preventive examinations and prove they are not suffering from chronic medical conditions, than not to identify them and start the medication process when the diseases progress. For future work, we plan to incorporate our additional criteria fully and run more simulations before implementing the update to the real system.

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EFEKAT COVID-19 KRIZE NA PRAĆENJE HRONIČNIH BOLESTI – PREDVIĐANJE PODATAKA KOJI NEDOSTAJU

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Pandemija COVID-19 imala je izrazito negativan uticaj ne samo na praćenje hroničnih bolesti nego i na prikupljanje podataka kroz medicinske informacione sisteme u ustanovama primarnog zdravstva. Opravdano, fokus je inicijalno prebačen na antipandemijske mere, dok je broj poseta vezanih za službu opšte prakse, posebno radi praćenja hroničnih bolesti, opao.

Sa manjim brojem raspoloživih podataka, algoritmi koji se bave identifikovanjem potencijalnih novih hroničnih bolesnika na osnovu prikupljenih zahteva postali su manje relevantni, a broj bolesnika koje više nije bilo moguće identifikovati je porastao.

U ovom radu prikazali smo unapređenje pomenutih algoritama za sumiranje podataka i identifikovanje hroničnih bolesnika kroz dodavanje novih kriterijuma za pretraživanje, koristeći mogućnosti integracije sa drugim medicinskim informacionim sistemima.

Unapređeni algoritam je evaluiran na podacima prikupljenim u Domu zdravlja u Nišu i upoređen sa rezultatima koje je dala inicijalna verzija algoritma.

Acta Medica Medianae 2023; 62(4):98-109.

***Ključne reči**: medicinski informacioni sistemi, sažetak istorije bolesti, hronične dijagnoze, identifikacija podataka koji nedostaju*

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NUTCRACKER SYNDROME IN CHILDREN: A SINGLE CENTRE EXPERIENCE

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Nutcracker syndrome (NS) is a rare cause of hematuria and/or proteinuria defined as the left renal vein entrapment between the abdominal aorta and the superior mesenteric artery. The majority of patients, mostly females, are diagnosed in puberty age. We report eight children diagnosed with NS analyzing their clinical features, diagnostics approaches, disease evolution and treatment outcomes.

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Key words: *nutcracker syndrome, hematuria, orthostatic proteinuria, left renal vein entrapment*

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Introduction

Nutcracker syndrome (NS) is a rare clinical condition where the renal vein is compressed between the abdominal aorta and the superior mesenteric artery (anterior type) (Figure 1 and Figure 2), or between the aorta and the vertebral column (posterior type) causing various symptoms in the patient. The existence of this state without expressing any symptoms is referred to as nutcracker phenomenon (1). The prevalence is not well known because this conditionis very frequently misdiagnosed. It is believed that NS is more frequently spread among young female population with a thin constitution. The prevalence of posterior NCS, also called pseudo-nutcracker syndrome, is much lower than the anterior one, ranging between 0.1% and 3.2% (2).

Most frequently patients experience one of the following symptoms or a combination of these symptoms: hematuria, proteinuria, left flank pain, chronic fatigue. The anatomical position of the left renal vein is going through the spine angle formed by the abdominal aorta and the superior mesenteric artery. If the angle is less than 45 degrees, as it is the case in thin, tall, young girls lacking fat tissue, then the left renal vein is entrapped within it causing proximal part of the vein dilatation following increased vein pressure (3). This condition is followed up by the interruption of the small vessels in the renal fornix causing hematuria, more likely microscopic than macroscopic. Renal vein congestion causes kidney swelling and stretching of the renal capsule, so some patients complain of left flank pain. The exact mechanism of proteinuria is unclear, but it is believed that vein obstruction changes renal hemodynamics. Renal venous stasis and venous hypertension decrease renal blood flow, which causes angiotensin II activation. Renin and aldosterone levels rise, resulting in an increase in efferent arteriolar resistance, which stimulates protein filtration (4).

As there are not precise diagnostic criteria for NS, before determining a diagnosis, it is necessary to exclude all other causes of hematuria or proteinuria (3). Radiology examinations must be performed to confirm the NS diagnosis. First choice should be renal Doppler ultrasound (5) as a non-invasive technique with sensitivity of 69 – 90% and specificity of 89 – 100% (6) after which a diagnostic approach could be completed with computed tomography (CT) and magnetic resonance imaging (MRI) (3, 1, 7).

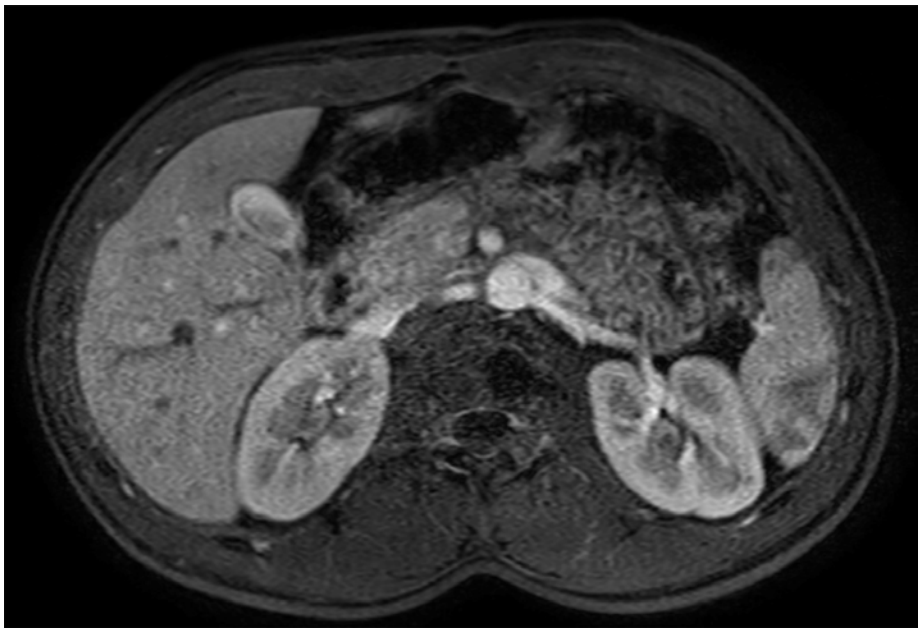

Figure 1. MRI angiography: proximal dilatation of the left renal vein, entrapped between the aorta and the superior mesenteric artery (transversal scan)

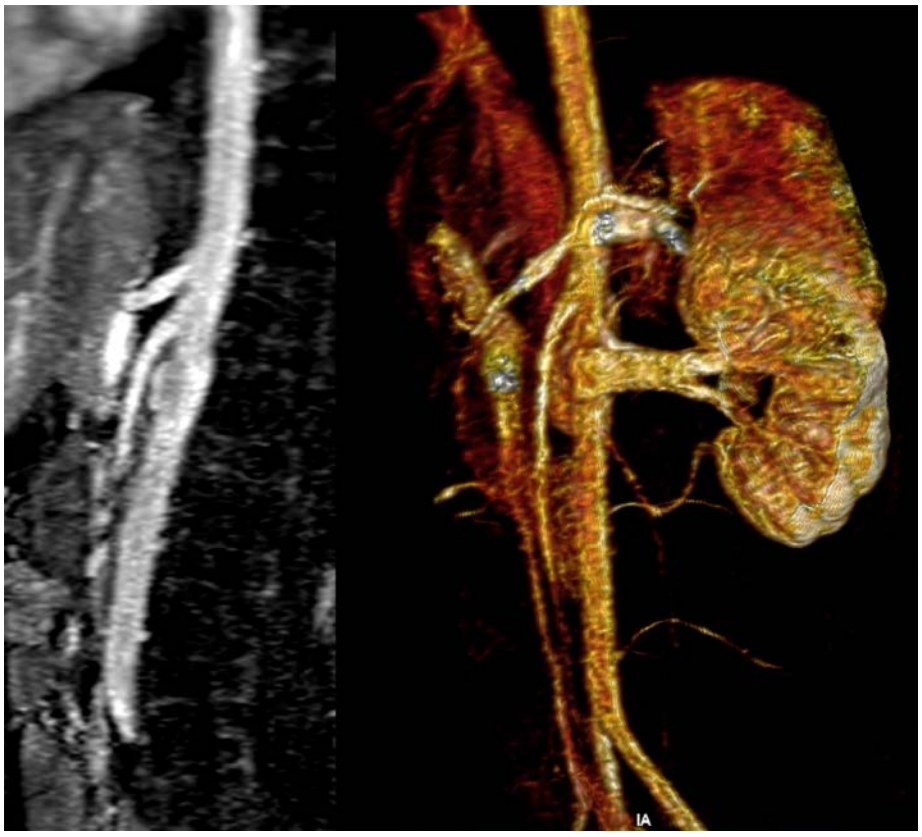

Figure 2. MRI angiography: proximal dilatation of the left renal vein, entrapped between the aorta and the superior mesenteric artery (axial scan)

The treatment of patients depends on severity of complaints and clinical features and can range from conservative methods to surgical approaches including balloon dilatation, LRV bypass, LRV transposition with or without wedge insertion between aorta and superior mesenteric artery, superior mesenteric artery transposition and, in the worst case, nephrectomy (1).

Material and Methods

We retrospectively reviewed eight adolescents, six females and two males, who were diagnosed with NS on MRI at the University Clinic Center Niš from January 2015 to December 2022. Their ages ranged from 13 to 17 years. All patients underwent physical examination, blood and urine analysis and radiologic examination (abdominal ultrasound, renal Doppler ultrasound and MRI angiography).

Results

Our study included eight patients who were diagnosed with NS at the Clinic of Pediatrics, University Clinical Centre Niš. Two of them were male (25%) and six (75%) were female. Their mean age was 14.87 years at diagnosis. Average body mass index was 19.8 kg/m^2. All patients were followed up for at least 15 months up to three years.

Clinical features of patients at diagnosis were analyzed (Table 1). Six (75%) patients showed isolated proteinuria with characteristics of orthostatic type and not nephrotic range. Five (83%) of them had daily proteinuria less than 500 mg, in one (17%) girl, the maximum value of proteinuria was 900 mg. Out of these six patients, three (50%) complained of occasional left flank pain, especially after excessive physical effort and they showed positive left renal succession. It is interesting that all patients presenting with isolated proteinuria were female.

Two patients had persistent microscopic hematuria with no episodes of macroscopic hematuria. They had no other symptoms and hematuria was revealed after routine urine sampling. Both patients were male.

Physical examination was normal in all patients, except for positive left renal succession in three girls with occasional left flank pain.

All patients underwent complete laboratory examination. Blood urea nitrogen, creatinine, electrolytes (sodium, potassium, calcium, phosphorus and magnesium), total protein, albumin, transaminases, C-reactive protein and vitamin D levels were within normal range. Calcium excretion and coagulation parameters were normal. Immunoglobulin A, M and G, antistreptolysin titer antibody, complement components C3 and C4 results were within referent range; antinuclear antibodies, anti-double stranded DNA antibodies and antineutrophil cytoplasmic antibodies results were negative.

Renal and urinary bladder ultrasonography revealed no pathological findings.

At the end, MRI was performed in all patients. MRI scan showed left renal vein narrowing in aortomesenteric clamp with diameter ratio before and after entrapment greater than 4.9 and angle between the abdominal aorta and the superior mesenteric artery was less than 30 degrees. Therefore, the NS diagnosis was confirmed with MRIafter ruling out other renal factors that may cause proteinuria and/or hematuria.

Table 1. Clinical characteristic of patients´

	Genderf-female m-male	Age (years)	BMI (kg/m^2)	Symptom	Clinical findings	24-hour urine protein excretion (mg)	Treatment	Disease evolution
1	f	14	19.0	none	proteinuria	440	conservative	no progression
2	f	15	19.4	left flank pain	proteinuria	500	conservative	no progression
3	f	17	20.9	none	proteinuria	850	conservative	improvement after weight gain
4	f	16	21.4	left flank pain	proteinuria	450	conservative	no progression
5	f	13	18.5	none	proteinuria	280	conservative	nephrotic syndrome
6	f	15	19.7	none	proteinuria	350	conservative	focal segmental glomerulosclerosis
7	m	15	18.7	none	microscopic hematuria	normal	conservative	no progression
8	m	14	21.1	none	microscopic hematuria	normal	conservative	no progression

The treatment of all patients was conservative. No medication was administrated after diagnosis. The follow-ups were done every three months and six of them showed no progression in clinical and laboratory findings. Two boys maintained microscopic hematuria with no other complications. Four girls showed no increase in proteinuria above 1 g daily during the following-up of two years. Two girls showed renal disease progression. One girl developed complete nephrotic syndrome shortly after being diagnosed with NS. The other girl showed up after 15 months with peripheral edema, hypertension, 2 g proteinuria daily and glomerular filtration rate of 78 ml/m^2/min; she underwent a renal biopsy, which confirmed focal segmental glomerulosclerosis. In both girls the treatment was started with corticosteroids, as they were diagnosed with glomerulopathy. The other six children were observed every three months without any medication and there was no disease progression in any of the cases.

Discussion

Nutcracker syndrome is a clinical phenomenon which occurs when the left renal vein is entrapped between the abdominal aorta and the superior mesenteric artery (anterior type), as well as between the aorta and the lumbarvertebral body (posterior type, pseudo-nutcracker syndrome) causing various symptoms, dominantly haematuria and/or proteinuria. The first type is much more frequent than the second one (8).

The exact prevalence of this state is unknown because of the lack of precise diagnostic criteria. It is believed that NS is more often diagnosed in female than in male, like in our study (75% of female versus 25% of male patients), although in some groups of patients the opposite proportion is described(9).

NS is diagnosed between the second and the seventh decade of life with the highest incidence in adolescents and young adults. This distribution is probably the consequence of rapid increase in body height in adolescence resulting in anatomical changes such as decreasing the angle between the abdominal aorta and the superior mesenteric artery. This is why thin, tall persons with low body mass index are more often diagnosed with NS (7). Some data suggest a positive correlation between low body mass index and NS (1). It is consistent with our result, where average BMI is below 20 kg/m^2.

The usual clinical features are hematuria, more likely microscopic, orthostatic proteinuria and left flank pain. Left renal entrapment leads to venous stasis and renal venous hypertension, which causes the rupture of the small veins into the renal calices. Macrohematuria is usually intermittent and mostly physical effort induced (9). In our group of patients, there were no evidence of macroscopic hematuria. Two patients (25%) had persistent microscopic hematuria following no complains and it was confirmed with a routine urine test.

Proteinuria presents mostly as orthostatic type and it is diagnosed witharoutine urine test. The exact mechanism of proteinuria is unclear, but it is believed that vein obstruction changes renal hemodynamics. Renal venous stasis and venous hypertension decrease renal blood flow, which causes the activation of angiotensin II. Renin and aldosterone levels rise resulting in an increase in the efferent arteriole resistance, which stimulates protein filtration (4). In our group of patients, isolated proteinuria was present in four (50%) patients, three (75%) of the mhad proteinuria less than 500 mg/24 h, in one girl (25%) it was 900 mg/24 h. Two patients had periodical left flank pain, most often exercise induced, two other patients had no complains. According to review studies data, proteinuria is present in non-nephrotic range, mostly below 1 g daily (5, 9).

In our study, two patients developed glomerulopathies during the follow-up period after being diagnosed with NS. A 13-year-old girl developed the nephrotic syndrome after three months, she was treated with corticosteroids and proteinuria resolved. A 15-year-old girl initially presented with asymptomatic mild proteinuria. Two years after being diagnosed, she developed hypertension and peripheral edema following 24-hour 2 g proteinuria and renal function impairment. However, she never came for a check-up since she did not experience any symptoms. She underwent renal biopsy and focal segmental glomerulosclerosis was proven.

In the literature, there are some reports of superimposed NS with other clinical entities, such as Henoch-Schonlein purpura, IgA nephropathy, membranous nephropathy, hypercalciuria and nephrolitiasis (3). Hirakawa et al. report a 21-year-old woman with coexisting NS and thin basement membrane disease clinically presenting with macrohematuria, proteinuria and left flank pain (10). Medin et al. described a 22-year-old man with IgA nephropathy and previous diagnosed NS in whom all symptoms disappeared and laboratory findings improved after steroid treatment (11). Some studies revealed high prevalence of NS in IgA nephropathies (6.8%), which suggests possible relationship between these two entities, but there have not been found hard evidence yet (12). Although hypertension is not a typical clinical feature of NS, several cases are described. Azhar et al. report a case of an 18-year-old Asian girl who presented with hypertension, hematuria and left flank pain and was diagnosed with NS after ruling out secondary causes of hypertension (13). But the connection between NS and hypertension is more likely in case described by Wang et al. where after the placement of endovascular stent in the left renal vein, blood pressure normalized within three days after surgical intervention (14). Superior mesenteric syndrome, also known as Wilkie's syndrome is a rare benign clinical entity emerging when the transverse part of the duodenum is compressed between aorta and superior

mesenteric artery causing duodenal stasis and gastrointestinal symptoms and it sometimes co-exists with NS (15, 16). So far, there has been no evidence about association of NS and focal segmental glomerulosclerosis in the available literature.

Diagnostic approach of NS must be based on the exclusion of all common causes of proteinuria, hematuria and left flank pain. To confirm the diagnosis, Doppler ultrasound should be performed as a first line radiology imaging method, eventually CT or MRI angiography. In our study, the diagnosis remained unclear after Doppler ultrasonography, so all patients underwent MRI angiography.

Treatment is recommended to be conservative if the clinical features are mild. The best treatment option for children is to follow-up them for at least two years as majority of them spontaneously recover. Some of patients with moderate proteinuria could be treated with ACE-inhibitors (1). In our group of patients, all patients were treated conservatively after diagnosis. Two girls, in whom disease got complicated by glomerulonephritis, were afterwards treated with steroids. The other six patients did not show disease progression. One girl experienced a decrease in moderate proteinuria after gaining weight. Pardinhas et al. reported seven patients diagnosed at adolescent age, all of them were treated conservatively with no medication and no recurrent symptoms reported during follow up (9). If clinical features of NS such as recurrent gross hematuria or severe abdominal pain are not tolerable, surgical treatment should be considered. The most successful surgical approaches include balloon dilatation, LRV bypass, renocaval reimplantation, LRV transposition with or without wedge insertion between aorta and superior mesenteric artery and superior mesenteric artery transposition (3). In the Serbian medical literature, Banzić et al. reported the first case of the NS presented with gross hematuria, which was resolved by reimplantation of the LRV into the more distal inferior vena cava (17).

Conclusion

Nutcracker syndrome is a rare entity accompanied by hematuria, proteinuria and other nonspecific symptoms. Its prevalence and prognosis, as well as possible complications are not well known because the NS is often misdiagnosed. As it most commonly occurs during puberty, pediatricians should consider NS as a possible cause of unexplained persistent or recurrent hematuria and orthostatic proteinuria.

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NUTCRACKER SINDROM KOD DECE – ISKUSTVO JEDNOG CENTRA

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Nutcracker sindrom (engl. *nutcracker syndrome* – NS) predstavlja redak uzrok hematurije i/ili proteinurije, a definisan je kao uklještenje leve bubrežne vene između abdominalne aorte i gornje mezenterične arterije. Kod većine bolesnika dijagnostikuje se u pubertetu, i to uglavnom kod žena. U radu se izveštava o osmoro dece sa dijagnozom NS-a. Analizirane su njihove kliničke karakteristike, kao i dijagnostički pristupi, ishodi lečenja i evolucija bolesti.

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***Ključne reči**: sindrom orašara, hematurija, ortostatska proteinurija, uklještenje leve bubrežne vene*

Review article

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BLEEDING ASSESSMENT TOOLS

Miodrag Vučić[1,2], Sanja Veličković[1], Božidar Lilić[1]

Bleeding Assessment Tools (BATs) are bleeding scoring systems used for screening and quantitative assessment of mild bleeding disorders. They consist of a standardized questionnaire and a scoring system that is used for the summation of the final score. In this review article, we have presented BATs that are applied in the area of hematology.

The earlier BATs were designed to distinguish patients with von Willebrand disease (VWD) from healthy individuals. Later modifications of the original Vicenza-BAT were developed in order to improve its specificity, precision, and flexibility, as well as to shorten the administration time. The most significant of these modifications is the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH-BAT), which is also validated for use in patients affected by hemophilia and inherited platelet disorders. ISTH-BAT score of ≥ 6 in adult females, ≥ 4 in adult males, and ≥ 3 in children is considered abnormal.

The WHO developed the first BAT for immune thrombocytopenia (ITP). However, more recently, the ITP International Working Group (IWG) designed the ITP-BAT. The IWG defines a severe or clinically relevant bleeding manifestation as an ITP-BAT SMOG index of S > 2 and/or M > 1 and/or O > 1. In 2016, a group of Chinese experts created a simple modification of the ITP-BAT, the ITP-2016. The values of the ITP-2016 Bleeding Score ≥ 5 indicate severe immune thrombocytopenia.

In the primary healthcare setting BATs serve as a valuable screening tool for discovering patients with bleeding disorders, who require further hematologic investigation.

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Key words: *scoring, von Willebrand disease, platelet disorders, hemophilia, immune thrombocytopenia*

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Introduction

Spontaneous termination of bleeding is realized through multiple interactions between vascular elements, thrombocytes, and coagulation factors (1).

If any of the aforementioned components is impaired, this might result in clinical manifestations of a bleeding disorder (2). While being utterly heterogeneous, both hereditary and acquired bleeding disorders share similar clinical manifestations, such as spontaneous bleeding events in various tissues and organs (2). Although generally rare in the overall population, unless a timely diagnosis is made, these disorders can greatly reduce the quality of life in affected patients (2).

Therefore, bleeding assessment tools (BATs) were designed in order to attain structured anamnestic data, and optimize the accuracy of a bleeding disorder diagnosis, as well as to predict the risk of bleeding events in the future (3).

BATs are bleeding scoring systems used for screening and quantitative assessment of mild bleeding disorders (2, 3). BATs are clinical tools consisting of a standardized questionnaire (based on structured bleeding symptomatology, which is quantified according to severity, and sometimes frequency), and a scoring system, that is used for the summation of the final score, and its interpretation (4).

BATs should be used primarily in the primary healthcare setting by trained medical professionals (general practitioners, pediatricians, trained nurses, and technicians), who are first to meet patients with a possible bleeding disorder (5). The final BAT score may help primary

healthcare providers decide whether the patient is in need of an examination by a hematology specialist and further laboratory testing, which can be expensive, time-consuming, and sometimes problematic for interpretation (3, 5).

An optimal BAT should be objective, highly specific and highly sensitive, validated on a real-life population, as well as accessible, available, short, and simple (6).

Even though no single BAT meets all of the aforementioned standards, the latest BATs tend to meet most of them (5).

When designing BATs and interpreting BAT scores it is important that medical profes-sionalsavoid mistaking trivial bleeding (defined as a bleeding which "causes no emotional distress, does not impair social life and activities, and does not require medical treatment") for significant bleeding symptoms (4, 6).

In this review article, we have presented a short review of BATs which are used in assessing bleeding disorders.

BATs used for von Willebrand disease type 1

Von Willebrand disease (VWD) is a bleeding disorder caused by either the dysfunction or deficiency of von Willebrand factor, a protein that enables the adhesion of platelets onto the subendothelial matrix and acts as the protector of FVIII (7).

VWD typically manifests itself through mucocutaneous bleeding events, especially during hemostatic challenges (surgery, tooth extraction, and postpartum bleeding) (7, 8).

Although there are basically three hereditary types of this disease (out of which type 2 is further divided into subtypes: 2A, 2B, 2M, 2N), VWD may rarely occur as an acquired condition, which is known as the acquired von Willebrand syndrome (7).

According to epidemiologic studies, the prevalence of VWD ranges between 1:100 and 1:10.000 individuals, making it the most frequent bleeding disorder (7, 9, 10).

VWD type 1, which results from a partial quantitative deficiency of VWF, accounts for 75% of individuals affected by von Willebrand syndrome (7).

Given its high prevalence as well as the pitfalls of the existing laboratory tests in cases of mild disease forms, a group of Italian investigators developed the Vicenza-BAT, the first BAT designed and validated for the screening of (mild forms of) VWD type 1 (5, 8). According to the severity of an individual bleeding symptom, each symptom included in the Vicenza-BAT was scored between 0 and 3 (11). The values of Vicenza-BAT bleeding score greater than 3 in adult males, as well as values greater than 5 in adult females, were associated with the phenotype of VWD (with specificity of 98%, and sensitivity of 69%) (6, 8, 11).

Since the main limitation of Vicenza-BAT was its relatively low sensitivity (as bleeding episodes that required higher intensity therapy were awarded higher scores), the next tool developed in order to improve sensitivity was the European Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD (MCMDM-1 VWD BAT) (5). Although MCMDM-1 VWD BAT improved sensitivity (100%), it was too complex and time-consuming (requiring approximately 40 minutes for administration) (5, 8, 11).

The Condensed MCMDM-1 VWD BAT was the later modification of the MCMDM-1 VWD BAT, which was significantly shorter, requiring only 10 minutes for administration (5, 8, 11). A normal range of the Condensed MCMDM-1 VWD BAT bleeding score ranges between -3 and +3, while abnormal values of the Condensed MCMDM-1 VWD BAT bleeding score are above 3 in both sexes (11).

In 2010, the International Society on Thrombosis and Hemostasis/Scientific and Standardization Committee (ISTH/SSC) Joint Working Group designed the ISTH-BAT (Tables 1 and 2) through the merging of the previously developed BATs, in order to improve the ease of use, precision, and flexibility (3, 4, 11). The ISTH-BAT was developed for the screening of mild bleeding disorders such as VWD, but it was later validated for the screening of mild hemophilia and inherited platelet disorders (3, 5). While previous BATs relied exclusively on the severity of bleeding symptoms, the ISTH-BAT also included quantitative elements regarding their frequency (11). Normal values of the ISTH-BAT Bleeding Score for adult females and adult males range between 0–5 and 0–3, respectively (11). This sex-related normal range difference is due to the inclusion of gender-specific bleeding symptoms (menorrhagia and postpartum bleeding) (6, 11). In the pediatric population (aged < 18 years), normal values of the ISTH-BAT bleeding score range between 0–2, regardless of sex (6, 11). In adult females the value of ISTH-BAT bleeding score ≥ 6 is considered "abnormal", whereas in adult males the value of ISTH-BAT bleeding score ≥ 4 is considered "abnormal", deserving further laboratory investigation (6, 11). In the pediatric population, ISTH-BAT bleeding score ≥ 3 is considered "abnormal", regardless of sex (6, 11). In the context of VWD, current guidelines of relevant medical organizations (ISTH, WFH, ASH, NHF) encourage the use of ISTH-BAT in a primary healthcare setting, while ISTH-BAT testing is considered unnecessary in a tertiary healthcare setting, as well as for patients with an existing family history of VWD (9, 12).

Self-BAT is a more recent self-testing version of ISTH-BAT, which can be filled out online (8, 9). Self-BAT has lesser specificity (23%) and greater sensitivity (78%) compared to the original ISTH-BAT (8).

Table 1. ISTH/SSC* definitions of bleeding symptoms included in the ISTH-BAT**

Bleeding symptom:	International Society on Thrombosis and Hemostasis/Scientific and Standardization Committee definition:
Significant epistaxis	lasting > 10 min; > 5 episodes/year; is not seasonal; not associated with an identifiable cause
Significant bruises:	≥ 5 bruises > 1 cm in exposed areas; petechiae; spontaneous hematomas
Significant minor cutaneous wound:	> 1 bleeding episode caused by superficial cuts lasting > 10 min requiring frequent bandage changes
Hematuria:	red to pale-pink coloration of urine that cannot be explained by the presence of a urologic disease
Hematemesis, melena, hematochezia:	gastrointestinal bleeding that cannot be explained by the presence of a specific disease
Significant oral cavity bleeding:	> 1 bleeding episode lasting > 10 min originating from the gums, bitten lips, cheeks, or tongue, causing swelling and frankly bloody sputum
Significant bleeding after tooth extraction:	any bleeding occurring after leaving the dentist's office, requiring a new, unscheduled visit or prolonged bleeding at the dentist's office causing a delay in the procedure or discharge
Significant surgical bleeding:	any bleeding judged by the surgeon to be abnormally prolonged, that causes a delay in discharge or requires supportive treatment
Menorrhagia:	criteria for significant menorrhagia may include any of the following: changing pads more frequently than every 2 h; menstrual bleeding lasting 7 or more days; and the presence of clots > 1 cm combined with a history of flooding. If a patient has previously made a record of her menstrual loss using a pictorial blood loss assessment chart (PBAC), a PBAC score > 100 also qualifies for a score of 1
Postpartum bleeding:	vaginal bleeding or uterine discharge (lochia) lasting > 6 weeks. Any bleeding lasting < 6 weeks that is judged by the obstetrician as abnormally heavy or prolonged, that causes a delay in discharge, requires supportive treatment, changing pads or tampons more frequently than every 2 h, or causes progressive anemia
Muscle hematomas/ hemarthrosis:	Any spontaneous joint/muscle bleeding (not related to traumatic injuries)
CNS bleeding:	subdural or intracerebral hemorrhage requiring diagnostic or therapeutic intervention is scored 3 or 4, respectively
Other bleeding symptoms:	when these bleeding symptoms occur during infancy, they are scored ≥ 1. Their presence when reported by either the patient or a family member should always prompt detailed laboratory investigation.

* The International Society on Thrombosis and Hemostasis/Scientific and Standardization Committee

** The International Society on Thrombosis and Hemostasis Bleeding Assessment Tool

Modified from Rodeghiero F, et al (4).

Table 2. The International Society on Thrombosis and Hemostasis Bleeding Assessment Tool Bleeding Score

Symptoms (up to the time of diagnosis)	POINTS				
	0*	1*	2	3	4
Epistaxis	No/trivial	> 5/year or > 10 min	Consultation only**	Packing/ cauterization/ antifibrinolytic	Transfusion or replacement therapy (use of hemostatic blood components and rFVIIa) or desmopressin
Cutaneous bleeding	No/trivial	For bruises 5 or more (> 1 cm) in exposed areas	Consultation only**	Extensive	Spontaneous hematoma requiring transfusion
Bleeding from minor wounds	No/trivial	> 5/year or > 10 min	Consultation only**	Surgical hemostasis	Transfusion, replacement therapy/desmo-pressin
Oral cavity	No/trivial	Present	Consultation only**	Surgical hemostasis/ antifibrinolyitic	Transfusion, replacement therapy/desmo-pressin
Gastro-intestinal bleeding	No/trivial	Present (not associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia)	Consultation only**	Surgical hemostasis/ antifibrinolyitic	Transfusion, replacement therapy/desmo-pressin
Hematuria	No/trivial	Present (macroscopic)	Consultation only**	Surgical hemostasis, iron therapy	Transfusion, replacement therapy/desmo-pressin
Tooth extraction	No/trivial or none done	Reported in ≤ 25% of all procedures, no intervention***	Reported in > 25% of all procedures, no intervention***	Resuturing/ packing	Transfusion, replacement therapy/desmo-pressin
Surgery	No/trivial or none done	Reported in ≤ 5% of all procedures, no intervention***	Reported in > 25% of all procedures, no intervention***	Surgical hemostasis/ antifibrinolytic	Transfusion, replacement therapy/desmo-pressin
Menorrhagia	No/trivial	Consultation only**/ changing pads more frequently than every 2 h /clot and flooding/ PBAC score > 100#	Time off work/school > 2 per year/ requiring antifibrinolytics/ hormonal/iron therapy	Requiring combined treatment with antifibrinolytics and hormonal therapy/ present since menarche and > 12 months	Acute menorrhagia requiring hospital admission and emergency treatment/ requiring transfusion, replacement therapy, desmopressin/ requiring dilatation and curettage or endometrial ablation or hysterectomy
Postpartum hemorrhage	No/trivial or no deliveries	Consultation only**/Use of syntocin /Lochia > 6 weeks	Iron therapy/ antifibrinolytic	Requiring transfusion, replacement therapy, desmopressin	Any procedure requiring critical care or surgical intervention (e.g. hysterectomy,

				or requiring examination under anesthesia and/or the use of uterine balloon/package to tamponade the uterus	internal iliac artery ligation, uterine brace sutures, uterine artery embolization)
Muscle hematomas	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or transfusion
Hemarthrosis	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or transfusion
CNS bleeding	Never	/	/	subdural, any intervention	Intrace−rebral, any intervention
Other bleedings##	No/trivial	Present	Consultation only**	Surgical hemostasis, antifibrinolytics	Transfusion/replacement therapy/ desmopressin

*Distinction between 0 and 1 is of critical importance. Score 1 means that the symptom is judged as present in the patient's history by the interviewer but does not qualify for a score 2 or more
**Consultation only: the patient sought medical evaluation and was either referred to a specialist or offered detailed laboratory investigation
***Example: 1 extraction/surgery resulting in bleeding (100%): the score to be assigned is 2; 2 extractions /surgeries, 1 resulting in bleeding (50%): the score to be assigned is 2; 3 extractions/surgeries, 1 resulting in bleeding (33%): the score to be assigned is 2; 4 extractions/surgeries, 1 resulting in bleeding (25%): the score to be assigned is 1
#If already available at the time of collection
##Include umbilical stump bleeding, cephalohematoma, cheek hematoma caused by sucking during breast/bottle feeding, conjunctival hemorrhage or excessive bleeding following circumcision or venipuncture. Their presence in infancy requires detailed investigation independently from the overall score.

ISTH-BAT Bleeding Score interpretation:
Normal values of ISTH-BAT Bleeding Score for adult males range between 0 and 3.
In adult males ISTH-BAT Bleeding Score ≥ 4 is considered "abnormal".
Normal values of ISTH-BAT Bleeding Score for adult females range between 0 and 5.
In adult females ISTH-BAT Bleeding Score ≥ 6 is considered "abnormal".
Normal values of ISTH-BAT Bleeding Score in the pediatric population (of both sexes aged < 18 years) range between 0 and 2.
In the pediatric population ISTH-BAT Bleeding Score ≥ 3 is considered "abnormal".

Modified from Rodeghiero F, et al (4).

BATs used for hemophilia

Hemophilia represents a group of bleeding disorders that are characterized by the deficiency of an intrinsic pathway coagulation factor (FVIII in hemophilia A, FIX in hemophilia B, and FXI in hemophilia C) (13, 14).

Although it is usually hereditary, hemophilia can rarely occur as an acquired autoimmune disease resulting from the development of anti-FVIII antibodies (inhibitors) (15).

The most common forms of hemophilia are X-linked recessive FVIII deficiency (hemophilia A) and FIX deficiency (hemophilia B) (13).

Both hemophilia A and B have identical clinical manifestations (typically hemarthroses, prolonged bleeding after tooth extraction), whereas depending on the degree of the coagulation factor deficiency, hemophilia can be mild, moderate, or severe (13).

In a study conducted by James et al., ISTH-BAT was evaluated in the context of recognizing hemophilia carriers (16). The results of this prospective study showed that the mean ISTH-

BAT score values achieved by hemophilia carriers were below those registered for females with VWD1, and above those achieved by VWD3 patients (16).

A multicenter Chinese study performed by Li et al., also confirmed the utility of the ISTH-BAT (as well as the Chinese-BAT, C-BAT) in discriminating hemophilia carriers from healthy females, since carriers achieved higher median bleeding scores (17). However, median scores from neither of the BATs showed a significant correlation with the levels of plasma coagulation factors (17).

According to the results of a recent study performed by Borhany et al., ISTH-BAT has proven itself to be useful in discriminating hemophilia (18). In the aforementioned study, ISTH-BAT was used for the assessment of a population of newly diagnosed, as well as already diagnosed patients with hemophilia A (78 patients) and B (37 patients), in order to establish the role of ISTH-BAT in the diagnostics and severity assessment, as well as to investigate the correlation between the ISTH-BAT score and plasma levels of the deficient coagulation factors in children and adults (18). By using ISTH-BAT, Borhany and colleagues were successful in discriminating hemophilia patients from healthy controls, since the bleeding score was significantly higher in hemophilia patients (18). Regarding the achieved ISTH-BAT score values, no significant difference was found in the hemophilia A and B patient subgroups, nor between the newly diagnosed and known hemophilia patients (18). This study also found that the ISTH-BAT score was higher in patients with severe hemophilia A compared to those with the mild form of this disease, as well as that children had a lower score compared to the adult patients (18).

BATs used for inherited platelet disorders

Inherited platelet disorders (IPDs) represent a heterogeneous spectrum of bleeding disorders that include defects of platelet functions and/or a decrease in platelet counts (3).

Gresele et al. performed a large multinational study in order to establish the diagnostic utility of ISTH-BAT in discriminating IPDs from healthy controls (3).

Additional aims of the aforementioned study were to distinguish VWD1 from inherited platelet function disorders (IPFDs) as well as various IPFDs by using ISTH-BAT (3).

The results from Gresele et al. proved that the values of the ISTH-BAT bleeding score above 6 in patients with a mucocutaneous bleeding diathesis, in whom VWD1 and coagulation disorders were excluded by using preliminary laboratory screening tests, indicate a diagnosis of IPFD with a 99% chance (3).

The ISTH-BAT bleeding score was significantly higher in IPFD patients (median bleeding score of 9) in comparison to VWD1 patients (median bleeding score of 5) (3).

The percentage of patients with an ISTH-BAT score > 2 (patients with clinically relevant bleeding symptoms) was significantly higher in IPFD patients in comparison to other study groups (3). This study also demonstrated that the median number of bleeding symptoms was lowest for healthy individuals (0) and those with inherited thrombocytopenias (1), and the highest in IPFD patients (4), while the median numbers of bleeding symptoms in individuals with VWD1 were in between (3).

The highest scores were recorded in the subpopulation of IPFDs (consisting mostly of Glanzmann thrombasthenia and CalDAG-GEFI-linked disorder cases), as well as in the subpopulation of inherited thrombocytopenias (consisting mostly of X-linked thrombocytopenia and TAR syndrome cases) (3).

It is important to note that the frequent association between inherited thrombocytopenias and platelet function defects causes the ISTH-BAT score values to be as high as in the case of IPFDs with a regular platelet count (3). In this case, the ISTH-BAT score would not support the diagnosis of an inherited thrombocytopenia given the severe bleeding tendency (3).

In order not to establish an incorrect diagnosis of an acquired thrombocytopenia, a high ISTH-BAT score in the presence of thrombocytopenia requires assessment of the medical history as well as a hematocytological analysis (19).

It was also recorded that certain bleeding events were more frequently recorded in certain bleeding disorders. Thus, VWD1 was associated with menorrhagia, and inherited thrombocytopenias were associated with cutaneous bleeding,
whereas IPFDs were associated more often with epistaxis (3).

Overall, ISTH-BAT is a useful tool capable of discriminating IPFD patients from healthy individuals (3). However, it is less reliable for distinguishing VWD1 from IPFDs, and between inherited thrombocytopenia and IPFDs (3). By using ISTH-BAT, it is impossible to distinguish patients affected by inherited thrombocytopenia from healthy individuals (3).

Although ISTH-BAT is not yet sufficiently validated in IPFDs, current IPFD guidelines suggest using ISTH-BAT for the sake of assessing the severity of bleeding symptoms and identifying patients who deserve further laboratory investigations (20).

BATs used for immune thrombocytopenia

Immune thrombocytopenia (ITP) is an acquired autoimmune disease that is characterized by the formation of antibodies against thrombocytic antigens (glycoproteins—gp IIb/IIIa, gp Ib/IX etc.), resulting in the excess destruction

of opsonized platelets by spleen macrophages and Kupffer cells and a decrease in platelet counts below 100 x 109/l (21).

Depending on the clinical course, ITP can be newly diagnosed (with a resolution within the next 3 months), persistent (with a resolution within a period of 3–12 months), or chronic (lasting longer than 12 months) (21, 22).

Although several specific BATs were developed in the past, the only one adopted for practical assessment of ITP in the context of clinical trials used to be a scale that was developed in 1981 on the initiative of the World Health Organization (23).

Since none of the previous BATs could meet the standards (simplicity, reproducibility, and clinical applicability) required for use in clinical practice, there was a need to design a new BAT that would be more clinically relevant (24).

In 2013, the International Working Group (IWG) on Immune Thrombocytopenia developed the Immune Thrombocytopenia Bleeding Assessment Tool (ITP-BAT, version 1.0), a clinically meaningful scoring system based on expert consensus (24). The IWG provided precise definitions for each of the ITP bleeding symptoms and grouped these symptoms into three domains: S—bleeding into the skin (which are the least dangerous), M—bleeding in the visible mucosae, and O—bleeding in organs and internal mucosae (which may be potentially life-threatening) (24).

Every bleeding symptom in each of the domains is further graded depending on its severity (24). Bleeding in the organ domain (except intracranial and ocular bleeding, which are graded from 0 and 2 to 4) and epistaxis have been graded between 0 (none) and 4 (24).

Other bleeding sites in mucosal and skin domains were graded into four grades (0–3), whereas any fatal bleeding was assigned a grade 5 (24).

Instead of obtaining a total sum ITP-BAT score, the IWG recommends reporting the 3 domains (S, M, and O) separately, thus generating the SMOG index, whereas intracranial bleeding should be reported separately (e.g., S2M2O3 (intracranial 3) stands for grade 2 for the skin domain, grade 2 for the visible mucosal domain, grade 3 for the organ and internal mucosal domain, and grade 3 for intracranial bleeding) (24).

The IWG defines a severe/clinically relevant bleeding manifestation as the ITP-BAT SMOG index of S > 2 and/or M > 1 and/or O > 1 (24).

The ITP-BAT version 1.0 was intended for describing bleeding manifestations in a form suitable for statistical analysis, in order to aid the investigations regarding ITP course, such as investigating the correlation between platelet counts and ITP manifestations (24).

Further prospective studies are still required in order to validate ITP-BAT for therapeutic decision-making (determining the effectiveness of the existing and innovative ITP treatments), as well as ITP prognosis (24).

Table 3. ITP-2016 (2016 Version of the Immune Thrombocytopenia Bleeding Grading System)

Points		1	2	3	5	8
Age	≥ 65 years	+				
	≥ 75 years		+			
Subcutaneous hemorrhage (petechiae/ecchymosis /hematoma)	head and face		+			
	other	+				
Mucosal hemorrhage (nasal cavity/gums/ oral mucosa/bloody bulla/conjunctive)	sporadic, automatic cease		+			
	frequent, hard to cease			+		
	with anemia				+	
Visceral (internal organs) hemorrhage (lung, gastrointestinal tract, urogenital system)	without anemia			+		
	with anemia				+	
	life threatening					+
	central nervous system					+

ITP-2016 Bleeding Score is calculated by summation of the age score and the bleeding manifestation score, which is the highest score among all achieved scores.

The values of ITP-2016 Bleeding Score ≥ 5 points indicate severe immune thrombocytopenia.

Modified from Thrombosis and Hemostasis Group (26).

The aim of a prospective study by Xiao et al. was to compare ITP-BAT to a new ITP bleeding scale—version 2016 (ITP-2016) (Table 3), which was developed by the Society of Hematology, Chinese Medical Association experts (25, 26).

A retrospective study conducted by Huang et al. compared the two BATs (ITP-BAT vs. ITP-2016) in assessing the population of Chinese pregnant ITP patients (27).

According to the results of this study, ITP-2016 appears to be more adequate for pregnant ITP patients of Chinese ethnicity (27).

The results of the aforementioned studies stated that, in comparison to ITP-BAT, ITP-2016 took less time to complete, while both BATs showed strong assessment consistency and adequate responsiveness (25, 27).

Both studies have demonstrated a negative correlation between platelet counts and the bleeding grade (25, 27).

These studies suggest that ITP-2016 represents a valid tool for the assessment of clinical manifestations and disease risk, as well as for the evaluation of (high-dose dexamethasone) treatment efficacy (25, 27).

The values of the ITP-2016 Bleeding Score ≥ 5 points indicate severe immune thrombocytopenia (26).

Conclusion

In light of possible issues with the interpretation of existing laboratory tests in diagnosing mild bleeding disorders, BATs remain useful tools for the clinical assessment of patients with potential bleeding disorders primarily in the primary healthcare setting, providing a standardized and structured approach for physicians who are less experienced in hematologic disorders.

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ALATI ZA PROCENU KRVARENJA

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Alati za procenu krvarenja (engl. *blood assessment tool* – BATs) predstavljaju sisteme bodovanja za krvarenja koji se koriste za skrining i kvantitativnu procenu blagih poremećaja krvarenja. Sastoje se od standardizovanog upitnika i sistema bodovanja koji se upotrebljava za računanje konačnog zbira bodova. U ovom preglednom članku predstavljeni su alati za procenu krvarenja koji se koriste u oblasti hematologije.

Prvi alati bili su dizajnirani radi razlikovanja bolesnika sa Fon Vilebrandovom bolešću od zdravih osoba. Kasnije modifikacije originalnog Vičenza alata razvijene su kako bi se poboljšale njegova specifičnost, preciznost i fleksibilnost i kako bi se skratilo vreme potrebno za popunjavanje upitnika. Najznačajnija od ovih modifikacija jeste alat Internacionalnog društva za trombozu i hemostazu (ISTH-BAT), takođe validiran za upotrebu kod hemofilije i urođenih bolesti trombocita. ISTH-BAT zbir ≥ 6 kod odraslih žena, ≥ 4 kod odraslih muškaraca i ≥ 3 kod dece smatra se abnomalnim nalazom.

Prvi alat za imunološku trombocitopeniju (engl. *immune thrombocytopenia*– ITP) razvila je Svetska zdravstvena organizacija (SZO). Međutim, nedavno je Internacionalna radna grupa (engl. *International Working Group*–IWG) za ITP razvila ITP-BAT. Radna grupa definiše teško / klinički relevantno krvarenje kao ITP-BAT SMOG index: S > 2 i/ili M > 1 i/ili O > 1. Modifikovanjem ITP-BAT tokom 2016. godine grupa kineskih eksperata razvila je ITP-2016. Vrednosti ITP-2016 zbira ≥ 5 odgovaraju teškoj imunološkoj trombocitopeniji.

Na nivou primarne zdravstvene zaštite alati za procenu krvarenja predstavljaju korisne skrining alate za otkrivanje bolesnika sa patološkim krvarenjima, koji zahtevaju sprovođenje dopunskih hematoloških pretraga.

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***Ključne reči**: bodovanje, Fan Vilebrova bolest, bolesti trombocita, hemofilija, imunološka trombocitopenija*

Original article

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IMAGE-GUIDED PERCUTANEOUS BIOPSY OF PERIPHERAL LUNG LESIONS: ULTRASOUND-GUIDED COMPARED TO CT-GUIDED BIOPSY

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Computed tomography (CT) guided percutaneous biopsy is well established technique used to provide tissue from the thoracic lesions, both in lung parenchyma and mediastinum. However, ultrasound (US) guided biopsy of peripheral thoracic lesions should not be underestimated because it has the advantage of real time control and the absence of radiation exposure.

In this retrospective study, which included 77 patients (59 men and 18 women) with peripheral lung lesions, we compared US and CT-guided biopsies analyzing the duration of the procedure, diagnostic accuracy, and complication rates, and we tried to determine correlation with needle diameter and lesion size.

Both techniques have successfully provided samples for histology diagnosis (95.65% with US and 90.32% with CT). There is a significantly higher rate of all complications, and especially major complications in CT-guided biopsies—22.58% versus 2.17% ($p < 0.001$). CT-guided procedure lasts significantly longer than US-guided procedure (42.48 ± 5.12 compared to 16.80 ± 3.42 minutes). There is also a significant negative correlation between lesion size and duration of the procedure in CT-guided biopsy: the smaller the lesion, the longer the duration of the procedure.

Although both techniques are very reliable and almost equally successful in obtaining samples for histopathology analysis, because of a higher rate of major complications and a longer duration of the procedure with CT guidance, ultrasound-guided biopsy should always be considered as the primary approach for peripheral lung lesions.

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Key words: *ultrasound, computerized tomography, thoracic biopsy, lung biopsy*

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Introduction

Lung cancer is recognized as a major public health issue, being the second most frequently diagnosed cancer and a leading cause of cancer-related mortality in men (1). The wider availability of CT (computed tomography) worldwide followed by an increased number of CT scans during the last two decades allowed for lung masses to be detected more frequently, but also while smaller in size, and in various locations (2). Some of these lesions are located peripherally. They remain a diagnostic challenge for pulmonologists, as flexible bronchoscopy and sputum cytology, although reliable for diagnosis of centrally located lesions, have limited value in diagnostics of peripherally located lesions (3–5). For lesions that are not accessible or remain unverified after bronchoscopy, the remaining alternatives for the acquisition of tissue samples are surgical biopsy and percutaneous biopsy. Percutaneous biopsy is certainly more popular, being minimally invasive and already proven successful and safe for several other organ systems (6), but to be precise, it has to be image-guided. Although CT is the method of choice for image guidance due to the high-resolution images it provides, it has been shown that for peripheral lesions both fluoroscopic and ultrasound-guided biopsies can provide good results (7–10). Ultrasound (US) can show masses in contact with the pleura but remains underestimated as a diagnostic method despite the fact that it has a high diagnostic value, provides real-time imaging, can be performed at the patient's bedside, and does not involve ionizing radiation (11–13).

Since there are limited data on US-guided biopsies of peripheral lung lesions, in this retrospective study we aimed to determine whether US has a role in image-guided biopsy of peripheral lung lesion comparing the results of US-guided and CT-guided transthoracic biopsy of these lesions in our institution, considering needle size (gauge), size of the lesion, duration of the

procedure, rate of complications, and success of the procedures.

Material and Methods

From January 2020 to December 2021, 107 transthoracic biopsies were performed in the Center for Radiology of the University Clinical Center of Niš, of which 46 were guided by ultrasound and 61 were guided by CT.

The criteria for inclusion in this retrospective study were the peripheral localization of the lesion in the lungs or mediastinum (which for research purposes was defined as a lesion up to 15 mm away from the pleura, or in direct contact with the pleura or with its invasion), while the exclusion criterion was the lack of imaging (previous CT examination) and accompanying medical documentation on the course of the disease before and on the course of hospitalization after the procedure.

One of the established indications suggested by guidelines for percutaneous transthoracic biopsy (14) was found in all of the patients. Before the biopsy procedure, all patients were examined for the presence of contraindications. Since there are no absolute contraindications, the medical records were reviewed and patients with image-characterized non-malignant lesions (vascular malformations, hydatid cysts, obvious inflammatory lesions) were not referred to biopsy, while on the basis of coagulation status, it was decided that some of the patients should have a coagulopathy correction.

Based on inclusion and exclusion criteria, 30 patients who underwent CT-guided biopsy were excluded from the study. Of the initial 107 subjects, 25 were not included because lesions were not peripheral, and 5 were excluded from the analysis because their records were incomplete or unavailable (as they were referred from other centers for biopsy).

Informed consent was acquired from all patients, after detailed informing on the procedure algorithm, possible complications and treatment. The records of the included patients were reviewed retrospectively.

The pre-procedural thoracic CT scans of 77 patients (46 for US-guidance, 31 for CT-guidance) and the size of the targeted lesions (the largest diameter was recorded) were reviewed. The lesions were divided into three groups based on the largest diameter (group I—SMALL ≤ 25 mm, group II—MEDIUM 26−50 mm, and group III—LARGE ≥ 51 mm).

All biopsies were performed by two interventional radiologists—CT-guided procedures on a GE multidetector computed tomography system—GE 64, while US-guided procedures were performed on a GE LOGIQ 7 ultrasound machine.

Patients were positioned regarding the location of the target lesion.

CT scanning was performed prior to biopsy, followed by measuring distances and determining the point of puncture.

An ultrasound-guided biopsy followed the analysis of the previously performed CT examination to determine the localization of the change, which was confirmed by an ultrasound examination of the pleural space and lungs with the use of a probe with a sterile sheath, and the puncture site was determined.

After cleaning and sterilizing the skin, and applying a local anesthetic, a minimal incision was made to ensure the passage of the needle. Needles with a diameter of 14 G, 16 G and 18 G were used (grouped into two groups—needles with a large gauge of 14 G and needles with a small gauge of 16 G and 18 G), which were introduced towards the lesion. Samples were taken by the automated BARD MAGNUM Multiple CORE Biopsy System (C. R. Bard, Inc. Bard Medical, Covington, Georgia) with appropriate CORE biopsy needles (C. R. Bard, Inc. Bard Medical, Covington, Georgia)—three samples per patient, if it was possible.

In the case of CT-guided biopsy, the needle was introduced, positioned and a control scan was performed until a satisfactory position was achieved, while in US-guided biopsy the needle was introduced under continuous control of the position in real-time. Immediately after the CT-guided biopsy procedure, control CT scans were performed, while after the US-guided biopsy, a US examination was performed.

The duration of the procedure was noted in the reports (measured in minutes from the moment the doctor approached the patient until the end of the procedure).

Control X-ray of the chest 4 hours after the procedure. Complications were noted in the reports.

Complications (pneumothorax, bleeding, hemoptysis, etc.) and interventions necessary for treatment were recorded. Depending on the presence of complications, they were divided into three groups: without complications, minor complications (hemoptysis, pulmonal hemorrhage, minimal pneumothorax) and major complications (pneumothorax requiring drainage, hemorrhage requiring blood transfusion).

The procedure was considered successful if the obtained samples allowed a histopathological diagnosis to be made.

Results

Transthoracic biopsy using the CORE biopsy system with an automatic gun was performed in 77 patients, for whom complete records were available. The average age of the patients was 62.50 ± 4.65 years; 18 of them (23.3%) were women and 59 (66.67%) were men. The longest axial diameter of the target lesions varied from 20 mm to 95 mm.

Tissue samples after transthoracic biopsy were obtained in all 77 patients (100%), of which the results were diagnostic in 72 (93.50%). Pathology results were non-diagnostic in 5 patients (6.49%).

Differences between CT- and US-guided biopsy were tested using the chi-square test. There were significant differences in needle diameter and complication rates between CT-guided and US-guided transthoracic biopsies of peripheral lung lesions (Table 1). Ultrasound-guided procedures allowed for larger gauge needles to be used (73.91% compared to 22.58% for CT-guidance) (and therefore larger samples) with a significantly lower rate of complications (15.21% compared to 54.84% for CT guidance). No complications were recorded in 84.79% of US-guided biopsies.

The difference in duration was tested by t-test (Table 2). The Kolmogorov Smirnov test confirmed normality in each procedure separately. The CT-guided procedure lasts significantly longer (42.48 ± 5.12 min compared to US-guided 16.80 ± 3.42 min).

The correlation was tested with the Spearman correlation coefficient (Table 3).

In CT-guided procedures, there was a significant negative correlation between the duration of the procedure and the size of the lesion (Rs = -0.846, sig = 0.000) - the smaller the lesion, the longer the procedure.

In the US-guided procedure, there was a significant negative correlation between the duration of the procedure and the size of the lesion (Rs = -0.841, sig = 0.000) - the larger the lesion, the shorter the duration of the procedure.

Between the size of the lesion and complications, there was no significant influence either with CT (sig = 0.177) or with US (sig = 0.618).

In CT-guided procedures, there was a significant negative correlation between the size of the lesion and the diagnosis (Rs = -0.395, sig = 0.028) - the larger the lesion, the lower the chance of diagnosis.

In US-guided procedures, there was a significant correlation between needle gauge and diagnosis (Rs = 0.359, sig = 0.014) – the larger the needle, the greater the chance of diagnosis.

Table 1. Relationship of US and CT guided biopsy with needle size, lesion size, complication rate and success of the procedure.

		IMAGE GUIDANCE		Total	Chi2	sig
		CT	US			
NEEDLE SIZE	LARGE BORE	7 (22.58%)	34 *(73.91%)*	41 (53.25%)	19.602a	.000
	SMALL BORE	24 (77.42%)	12 (26.09%)	36 (46.75%)		
LESION SIZE (mm)	SMALL	6 (19.35%)	4 (8.7%)	10 (12.99%)	1.942a	.379
	MEDIUM	14 (45.16%)	22 (47.83%)	36 (46.75%)		
	LARGE	11 (35.48%)	20 (43.48%)	31 (40.26%)		
COMPLICATIONS	NO	14 (45.16%)	39 *(84.78%)*	53 (68.83%)	14.937a	.001
	MINOR	10 *(32.26%)*	6 (13.04%)	16 (20.78%)		
	MAJOR	7 *(22.58%)*	1 (2.17%)	8 (10.39%)		
HP DIAGNOSIS	NO	3 (9.68%)	2 (4.35%)	5 (6.49%)	.866a	.352
	YES	28 (90.32%)	44 (95.65%)	72 (93.51%)		

Table 2. Comparison of US and CT guided biopsy procedure duration

		N	Mean	Std. Deviation	t	sig
PROCEDURE DURATION (min)	CT	31	42.48	5.12	24.489	.000
	UZ	46	16.80	3.42		

Table 3. Correlation of needle and lesion size with procedure duration and complication rate for US and CT guided biopsy.

			PROCEDURE DURATION	COMPLICATIONS	HP DIAGNOSIS
CT	NEEDLE GAUGE	Rs	-.635**	.084	-.345
		sig	.000	.655	.057
	LESION SIZE	Rs	-.846**	-.288	-.395*
		sig	.000	.117	.028
US	NEEDLE GAUGE	Rs	-.009	.251	.359*
		sig	.951	.092	.014
	LESION SIZE	Rs	-.841**	-.076	-.232
		sig	.000	.618	.120

Discussion

Determining adequate image modality for biopsy guidance of peripheral lung lesions is a very important issue for any specialist performing them since it can influence the outcome, success of the procedure and probability of complications. Our results demonstrate that ultrasound should be assessed and can be used as a reliable guiding modality in cases where the targeted lesion can be visualized by it (as in lesions in contact with or affecting the pleura). We confirmed that ultrasound is safer, less time-consuming, and equally (or even more) reliable than CT for peripheral lesions.

In our study, all lesions were 20 mm or larger (in measured diameter). The overall diagnostic reliability was noted to be very high with 2–3 samples obtained during each biopsy (15), totaling 93.51%. In 6.49% of our cases, the tissue samples were not diagnostic, the reasons for which were considered to be sampling errors—missed lesions, taking samples from the necrotic center or peritumoral inflammatory zones. In different studies the reported reliability for US-guided biopsies varies from 64% to 97% (10, 12, 13, 16, 17) compared to CT-guidance varying from 80% to 95% (7, 8, 9). Our results are in accordance with literature data, and we confirmed that as an imaging modality used for guidance, US (95.65%) was slightly more reliable than CT (90.32%). This can also be explained by the possibility of using large diameter needles when guiding the procedure with ultrasound (73.91%) (since lesions were adjacent to pleura) compared to CT (22.58%).

By comparative analysis of US- and CT-guided biopsies, we concluded that the total number of all complications, especially major ones, is significantly higher in CT-guided biopsies, up to 22.58% (compared to 2.17% in US-guided biopsies—this is somewhat expected because in our study CT-guided punctures targeted both peripheral lesions that are pleural-based and those not in direct contact with the pleura but within 15 mm distance from pleura, which in itself increases the risk of complications). The rate of pneumothorax is significantly lower in the literature, ranging from 1% to 5% (9, 13), compared to ours (overall 10.39%). This can be explained by our technique that is not based on coaxial introducers and by our use of larger gauge needles compared to others (18, 19). The total number of major complications in our study was 8 (10.38%), and all patients with major complications had a massive pneumothorax that was drained and therefore prolonged hospitalization, but of all these patients, only one underwent US-guided biopsy.

Apart from described and reported safety benefits of US guidance, our study determined that CT-guided procedures last significantly longer than US-guided procedures (42.48 ± 5.12 min versus 16.80 ± 3.42 min, respectively), which can be explained by the depth of the lesions but above all by the imaging capabilities of monitoring the US-guided procedure in real-time. The literature also reports a shorter duration of US-guided procedures (13), with time-saving effects varying from 20% to 42% (13, 20, 21). It seems that in our study the time-saving effect was higher, but it was not calculated, and it was probably based on previous CT existing in every patient, which allowed for faster US localization of the lesion.

Our results showed a statistically significant correlation of complications (major pneumothorax requiring drainage) with CT-guided biopsies (Table 1) and a correlation of procedure duration with lesion size (Table 2), suggesting that smaller diameter lesions require longer procedure time when using CT guidance. Heerink et al. (22) also found that with the growth of the lesion, the probability of obtaining a diagnostic sample is lower due to the high probability of necrotic parts of the change, which was confirmed by our study (Table 3).

Conclusion

Our study shows that the diagnostic reliability of ultrasound-guided biopsy of peripheral lung lesions is approximately equal to the reliability of CT-guided biopsy, with a significantly lower complication rate and significantly shorter procedure duration. Since it is performed without ionizing radiation, it has a shorter overall procedure duration, and is equally (or more) accurate, ultrasound-guided lung biopsy should be considered as a standard procedure and a viable, even more favourable alternative to CT-guided biopsy for peripheral lesions that affect pleura, in case there is a specialist who can perform it and if the lesion is easily visualized by ultrasound.

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PERKUTANA BIOPSIJA PERIFERNIH LEZIJA PLUĆA VOĐENA SLIKOM: POREĐENJE BIOPSIJE VOĐENE ULTRAZVUKOM I BIOPSIJE VOĐENE KOMPJUTERIZOVANOM TOMOGRAFIJOM

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Perkutana biopsija vođena kompjuterizovanom tomografijom (engl. *computed tomography* – CT) dobro je ustanovljena tehnika za pribavljanje uzoraka iz promena grudnog koša, pluća i medijastinuma. Međutim, zbog prednosti koje ultrazvučno vođena biopsija ima u kontroli procedure u realnom vremenu i odsustva jonizujućeg zračenja, ne treba je potcenjivati. Cilj ove studije, koja je obuhvatila 77 bolesnika (59 muškaraca i 18 žena) sa perifernim promenama pluća, bio je da utvrdi odnos ultrazvučno vođene biopsije i biopsije vođene CT-om upoređivanjem trajanja intervencije, dijagnostičke uspešnosti i stope komplikacija, kao i ispitivanjem njihove povezanosti sa veličinom promena i prečnikom igle.

Histološka dijagnoza je uspešno postavljena obema tehnikama (95,65% kod ultrazvuka (UZ), odnosno 90,32% kod CT-a). Postoji statistički značajna razlika između stope komplikacija i načina vođenja procedure; evidentiran je značajno veći broj svih, a posebno teških komplikacija, kod biopsija vođenih CT-om – 22,58% spram 2,17% ($p < 0,001$). Procedura vođena CT-om traje znatno duže od one vođene UZ-om (42,48 minuta ± 5,12 minuta naspram 16,80 minuta ± 3,42 minuta). Utvrđeno je da postoji značajna negativna korelacija između veličine lezije i trajanja procedure kod biopsije vođene CT-om: što je manja lezija, to duže traje procedura.

Iako su obe tehnike veoma pouzdane i skoro jednako uspešne u obezbeđivanju adekvatnih uzoraka za postavljanje histološke dijagnoze, s obzirom na veću stopu teških komplikacija i duže trajanje procedure prilikom vođenja CT-om, kod perifernih promena u plućima uvek treba prvo razmotriti biopsiju vođenu UZ-om.

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***Ključne reči**: ultrazvuk, kompjuterizovana tomografija, torakalna biopsija, biopsija pluća*

Original article

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EFFECTS OF EXERCISE TRAINING ON THE DOUBLE PRODUCT AND QT DISPERSION IN PATIENTS AFTER MYOCARDIAL INFARCTION: WHETHER THE LEFT VENTRICULAR EJECTION FRACTION HAS AN EFFECT ON THE BENEFIT

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The aim of this study was to examine the effect of exercise training on the double product (DP) and QT dispersion in patients after myocardial infarction and to determine whether the left ventricular ejection fraction (LVEF) had an effect on the benefit.

A total of 375 patients with previous MI were included in the study. Patients were randomly divided into a group that was included in the exercise training program (TG: 329 patients) and a group that did not train (NTG: 46 patients). All patients underwent an echocardiographic examination, standard ECG, corrected QT dispersion (QTdc) and exercise test, after which the training group was included in the exercise training program lasting 21 days.

Reduced left ventricular ejection fraction (RLVEF), less than 40%, was registered in 104 (31.6%) patients in TG, while in NTG it was registered in 16 (34.8%). At the beginning of the follow-up period, in TG, there was no significant difference in DP values, between patients with and without RLVEF (p-NS), while QTdc values were significantly higher in those with RLVEF ($p < 0.001$). After 21 days in TG, a significant decrease in DP (12.3 ± 1.8 vs. 11.7 ± 1.3 beat/min x mm Hg $x10^3$; $p < 0.01$) and QTdc (103.6 ± 28.3 vs. 96.1 ± 25.8 ms; $p < 0.05$) was registered in patients with RLVEF and a significant decrease in DP (11.9 ± 2.2 vs. 10.8 ± 1.6 beat/min x mmHg $x10^3$; $p < 0.001$) and QTdc (65.7 ± 25.4 vs. 58.6 ± 22.8 ms; $p < 0.005$) in those without RLVEF. In NTG patients, after a follow-up period of 21 days, no significant changes in DP and QTdc parameters were registered.

The results show that exercise training has a beneficial effect on DP and QT dispersion in patients with previous MI. LVEF has a significant influence on the benefit of exercise training, patients without RLVEF have a better benefit.

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Key words: *exercise, double product, coronary disease, QT dispersion, left ventricular ejection fraction*

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Introduction

Patients with previous myocardial infarction (MI) are at high risk for new adverse cardiovascular events, including cardiac death (1). After a myocardial infarction, patients have a significant reduction in physical exercise capacity, which is caused by damage to the myocardium and prolonged bed rest. Long-term physical inactivity leads to the weakness of skeletal muscles, damage to peripheral circulation and dysfunction of the autonomic nervous system. A decrease in physical exercise capacity leads to an increase in heart rate at rest and various forms of psychological disturbances. The significance of the reduction in physical exercise capacity mostly depends on the length of rest and the degree of the left ventricle dysfunction. The reduction of exercise tolerance is a consequence of reduced left ventricular function and skeletal muscle weakness, which is caused by reduced skeletal muscle perfusion and a significant increase in peripheral resistance. Increased heart rate at rest and inadequate increase in heart rate during exertion

is the result of autonomic nervous system dysfunction. Mental problems in the form of depression and anxiety are a significant risk factor in patients with previous MI (2).

Exercise training in patients with previous MI improves physical exercise capacity, left ventricular function, has a positive effect on the patient's psychological status, reduces total mortality by 20%, cardiac mortality by 26% and reinfarction by 20% (3).

There are many causes for left ventricular dysfunction, but the most common reason is coronary disease. In patients with MI, abnormal movements of the left ventricular wall occur in the form of hypokinesia, akinesia, and dyskinesia due to the disturbance of the contractile function of the infarct zone. In patients with MI, the degree of reduction in left ventricular function depends on the size of the infarct zone. A reduction in diastolic compliance occurs if the infarction has affected eight percent of the left ventricular mass. When the contraction abnormality exceeds 15% of the left ventricular mass, there is a decrease in left ventricular ejection fraction (LVEF) and an increase in end-diastolic and end-systolic volume. Clinical signs of left ventricular dysfunction occur when the contraction abnormality exceeds 25%, and cardiogenic shock occurs when the infarction affects more than 40% of the left ventricular mass (4, 5).

Controlled exercise training has beneficial effects in patients with NIHA class I–III. An aerobic, dynamic type of exercise is recommended, such as riding a stationary or regular bicycle and walking. Aerobic training should be performed for 30–60 minutes, preferably 3–5 times during the week, and interval training is preferred. Patients in whom physical training does not improve physical capacity have a poor prognosis (6–8).

After an MI, a significant percentage of patients die of sudden cardiac death. In the Framingham study during a follow-up period of 30 years, sudden cardiac death was 6.7 times more common in coronary patients compared to other people (9).

QT dispersion (QTd) reflects heterogeneity in the repolarization of the myocardium and is a marker of myocardial ischemia and electrical instability, reflecting increased susceptibility to ventricular arrhythmias. According to numerous studies, QTd is an independent prognostic marker for arrhythmic events, cardiac mortality and sudden cardiac death, especially in coronary patients (10–12).

Given that QTd is an important prognostic marker in coronary patients and that patients after myocardial infarction are at high risk of new adverse cardiovascular events, the aim of this study is to examine the effect of exercise training on the double product (DP) and QT dispersion in patients after myocardial infarction and to determine whether the left ventricular ejection fraction has an effect on the benefit.

Material and methods

The research occurred at the Institute for Treatment and Rehabilitation Niška Banja, Niš, Serbia.

A total of 375 patients (96 females and 279 males), mean age 56.5 years, with previous MI, were included in the study, within 3 months after MI. Inclusion criteria were that patients were in sinus rhythm and free of atrioventricular blocks also no bundle branch blocks. Patients were randomly divided into a group that was included in the exercise training program (TG: 329 patients) and a group that did not train (NTG: 46 patients). Patients were of similar site of infarction and also had similar duration of baseline exercise test.

All patients underwent laboratory analyses, echocardiographic examination, standard ECG, corrected QT dispersion (QTdc) and an exercise test, after which the training group was included in an exercise program lasting 21 days.

Based on the results of the exercise test, the patients of TG received instructions for the degree of exercise activity. Patients were instructed to perform gymnastic exercises, use a bicycle ergometer and walk. Patients were also instructed not to change drug therapy during the 21-day follow-up period, after which laboratory tests, ECG, and exercise tests were performed again.

The QT interval was measured from a standard ECG, from the beginning of the QRS complex to the end of the T wave, where it joined the isoelectric line. The QT interval was measured in all ECG leads, and it was necessary to be able to measure a minimum of 8 leads for the patient to be included in the study. Bazett's formula was used to correct the QT interval according to heart rate (13). QTd was calculated as the difference between the maximum and minimum values of the QT interval found in any of the 12 ECG leads. The difference between the maximum and minimum corrected values of the QT interval, found in any of the ECG leads, is obtained from corrected QTd (QTdc).

Exercise tests were performed on all patients on a treadmill according to the Bruce protocol (14). The load tests were limited by submaximal heart rate (85% of the maximum heart rate), as well as the appearance of symptoms, complex heart rhythm disorders, and also the appearance of electropathological changes on the ECG. The following ECG criteria were used for a positive exercise test: the presence of horizontal or down-sloping ST segment depression ≥ 1mm; ST segment elevations ≥ 1 mm in leads without Q waves.

Echocardiographic examinations were performed in all patients while they were lying in the left lateral decubitus position. The M-mode technique, two-dimensional echocardiography and Doppler echocardiography, with the use of color Doppler, were used. A Siemens Acuson SC 2000 was used for echocardiographic examination. Measurement of the dimension of the left

ventricle, and left ventricular wall thickness was performed using the M-mode technique with verification using a two-dimensional method, according to the criteria of the Penn Convention (15). LVEF was determined using two-dimensional echocardiography using the Simpson method (16).

Statistical Analyses

The values of the monitored parameters of the study groups are expressed as mean value ± SD. We compared clinical and biochemical data using the Student's t-test (expressed as mean value ± SD). Complete analyses were performed using software - SPSS v25 (SPSS, Chicago, IL, United States) with a statistical significance level set at $p \leq 0.05$.

Results

Reduced left ventricular ejection fraction (RLVEF), less than 40%, was registered in 104 (31.6%) patients in TG, while in NTG it was registered in 16 patients (34.8%).

At the beginning of the follow-up period, in TG, there was no significant difference in DP values, between patients with and without RLVEF, while QTdc values were significantly higher in those with RLVEF, Table 1.

After 21 days in TG, a significant decrease in DP, QTdc, total cholesterol, as well as LDL cholesterol was registered in patients with RLVEF, Table 2. TG with RLVEF achieved a significantly longer time in the second exercise test, Table 2.

After a 21-day follow-up period, in TG, a significant decrease in DP, QTdc, total cholesterol, as well as LDL cholesterol was registered in patients without RLVEF, Table 3. TG without RLVEF achieved a significantly longer time in the second exercise test, Table 3.

In NTG patients, after a follow-up period of 21 days, no significant changes in DP and QTdc parameters were registered, Table 4.

Table 1. Comparison of QTdc and double product in training group patients after myocardial infarction with and without reduced left ventricular ejection fraction, before starting with the program of physical training

Parameters	Patients after MI with RLVEF	Patients after MI without RLVEF	P
N	104	225	
Age (years)	57.3 ± 10.3	55.9 ± 9.5	NS
QTdc (ms)	103.6 ± 28.3	65.7 ± 25.4	0.001
DP (beat/min x mm Hg x10^3)	12.3 ± 1.8	11.9 ± 2.2	NS

QTdc- corrected QT dispersion; DP- double product; MI- myocardial infarction, RLVEF- reduced left ventricular ejection fraction

Table 2. Comparison of monitored parameters in the training group patients after myocardial infarction with reduced left ventricular ejection fraction before and after short-term exercise training

Parameters	Before short-term exercise training	After short-term exercise training	P
N	104	104	
QTdc (ms)	103.6 ± 28.3	96.1 ± 25.8	0.05
DP (beat/min x mmHg x10^3)	12.3 ± 1.8	11.7 ± 1.3	0.01
Total cholesterol (mmol/L)	5.2 ± 1.0	4.9 ± 1.2	0.05
LDL cholesterol (mmol/L)	2.9 ± 0.4	2.8 ± 0.3	0.05
Glycemia (mmol/L)	5.1 ± 1.1	4.8 ± 0.8	0.02
Time achieved on the exercise test (min)	4.9 ± 2.2	5.7 ± 1.9	0.005

QTdc- corrected QT dispersion; DP- double product

Table 3. Comparison of monitored parameters in the training group patients after myocardial infarction without reduced left ventricular ejection fraction before and after short-term exercise training

Parameters	Before short-term exercise training	After short-term exercise training	P
N	225	225	
QTdc (ms)	65.7 ± 25.4	58.6 ± 22.8	0.005
DP (beat/min x mmHg x10^3)	11.9 ± 2.2	10.8 ± 1.6	0.001
Total cholesterol (mmol/L)	5.0 ± 1.6	4.7 ± 1.3	0.025
LDL cholesterol (mmol/L)	2.8 ± 1.0	2.6 ± 0.8	0.02
Glycemia (mmol/L)	5.1 ± 1.8	4.7 ± 1.1	0.005
Time achieved on the exercise test (min)	5.3 ± 1.6	8.1 ± 1.8	0.001

QTdc- corrected QT dispersion; DP- double product

Table 4. Comparison of monitored parameters in the non-training group patients after myocardial infarction before and after a follow-up period of 21 days

Parameters	Before the follow-up period of 21 days	After the follow-up period of 21 days	P
N	46	46	
QTdc (ms)	76.9 ± 23.5	74.8 ± 25.6	NS
DP (beat/min x mm Hg x10^3)	12.1 ± 1.9	11.9 ± 1.7	NS
Total cholesterol (mmol/L)	5.1 ± 1.4	5.0 ± 1.7	NS
LDL cholesterol (mmol/L)	2.8 ± 0.8	2.8 ± 0.9	NS
Glycemia (mmol/L)	5.0 ± 1.9	4.9 ± 1.8	NS
Time achieved on the exercise test (min)	5.2 ± 2.4	5.8 ± 2.7	NS

QTdc- corrected QT dispersion; DP- double product

Discussion

An increased QTd reflects the regional difference in myocardial repolarization, and is also a prognostic marker for cardiac death in coronary patients (17–19). Our study showed that, before the start of exercise training treatment, patients after MI and RLVEF had significantly higher QTdc values compared to those without RLVEF. The left ventricle systolic function has a significant influence on the values of the QT dispersion parameters. A significant correlation between QTdc and LVEF in coronary patients has been shown (20). In coronary patients, fibrotic changes and myocardial ischemia reduce left ventricular function, increase sympathetic activity, directly through myocardial ischemia and reflexively through pressoreceptors, and reduce vagus activity and thus increase the dispersion of repolarization. It has been proven that the administration of noradrenaline significantly increases the values of QTd. In patients with heart failure, increased QTd values can identify those at high risk of cardiac death (21–23).

The results of our study indicate that after exercise training treatment in patients after MI, there is a significant reduction in QTdc values in both patients with RLVEF and those without RLVEF. A more significant decrease in QTdc was found in patients after MI without RLVEF. The greatest impact on the reduction of QTd is the improvement of the function of the autonomic

nervous system since it has been shown that physical training significantly increases vagus tone and decreases sympathetic tone (24, 25). It is likely that the improvement in collateral blood flow in the myocardium contributed to the decrease in QTd parameters since ischemia has been proven to increase QTd. After successful reperfusion, in patients with acute MI, as well as in those with chronic myocardial ischemia, there is a significant decrease in QTd (26–29).

DP is an indirect indicator of myocardial oxygen consumption (30). The results of our study indicate that in post-MI patients, after exercise training treatment, a significant reduction in double product at rest was noted. The decrease in DP was more pronounced in those without RLVEF. This reduction of the double product reduces the demand of the myocardium for oxygen, as a result of which the time until the onset of angina pain in coronary patients is prolonged, and it is also a significant prognostic indicator in patients after MI (31).

After the exercise training program, a significant decrease in total cholesterol, as well as LDL cholesterol was registered in our patients after MI. In post-MI patients, lipid lowering due to statin therapy significantly increases survival and reduces cardiac mortality (2). The reduction of total cholesterol as well as LDL cholesterol in our patients after MI indicates the great importance of exercise training. Risk factors for cardiovascular diseases affect the speed of development of atherosclerosis. It is of great importance whether one or more risk factors are present, as well as their duration. Statins are first-line drugs for lowering LDL cholesterol, which should be included immediately (2, 32). Statin therapy reduces the level of LDL cholesterol and circulating highly sensitive CRP, improves endothelial function, reduces thrombogenesis and inflammatory components of arterial atheroma, and stabilizes atheromatous plaques (32).

A significant increase in exercise capacity was observed in our post-MI TG patients after exercise treatment. These patients achieved a significantly longer time and a higher level of load in the second exercise test.

Conclusion

The results show that exercise training has a beneficial effect on DP and QT dispersion in patients with previous MI. The left ventricular ejection fraction has a significant influence on the benefit of exercise training, patients without RLVEF have a better benefit. In patients after MI, exercise training significantly reduces myocardial oxygen consumption at rest and probably reduces the possibility of arrhythmias, more so in those without RLVEF.

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EFEKTI FIZIČKOG TRENINGA NA DVOJNI PROIZVOD I QT DISPERZIJU KOD BOLESNIKA SA PREŽIVELIM INFARKTOM MIOKARDA – DA LI EJEKCIONA FRAKCIJA LEVE KOMORE IMA UTICAJA NA BENEFIT

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Cilj ovog rada bio je da se utvrdi efekat fizičkog treninga na dvojni proizvod (eng. *double product* – DP) i QT disperziju kod bolesnika sa preživelim infarktom miokarda (eng. *myocardial infarction* – MI) i da se ispita da li ejekciona frakcija leve komore (eng. *left ventricular ejection fraction* – LVEF) ima uticaja na benefit od fizičkog treninga.

U studiju je bilo uključeno 375 bolesnika sa preživelim MI. Bolesnici su potom podeljeni u dve grupe – u jednoj grupi bili su bolesnici uključeni u program fizičkog treninga (TG: 329 bolesnika), dok su drugu grupu činili bolesnici koji nisu trenirali (NTG: 46 bolesnika). Svim ispitanicima urađeni su ehokardiografski pregled, dvanaestokanalni EKG, korigovana QT disperzija (QTdc) i test opterećenja. Nakon toga, ispitanici iz TG uključeni su u program fizičkog treninga u trajanju od tri nedelje.

Redukovana ejekciona frakcija leve komore (eng. *reduced left ventricular ejection fraction* – RLVEF), manja od 40%, bila je prisutna kod 104 (31,6%) bolesnika u TG i kod 16 bolesnika (34,8%) u NTG. Na početku perioda praćenja, u TG nije bilo značajne razlike u vrednostima DP-a između bolesnika sa RLVEF-om i onih bez RLVEF-a (p-NS), dok su QTdc vrednosti bile značajno veće kod bolesnika sa RLVEF-om ($p < 0,001$). Posle tri nedelje, u TG uočena je značajna redukcija QTdc (103,6 ± 28,3 prema 96,1 ± 25,8 ms; $p < 0,05$) i DP-a (12,3 ± 1,8 prema 11,7 ± 1,3 otkucaja/min x mmHg $x10^3$; $p < 0,01$) kod bolesnika sa RLVEF-om. Značajna redukcija QTdc (65,7 ± 25,4 prema 58,6 ± 22,8 ms; $p < 0,005$) i DP-a (11,9 ± 2,2 prema 10,8 ± 1,6 otkucaja/min x mmHg $x10^3$; $p < 0,001$) zapažena je i kod bolesnika bez RLVEF-a. Nasuprot tome, u NTG nije bilo bitnijih promena.

Rezultati su pokazali da fizički trening ima povoljan uticaj na DP i QTdc kod bolesnika sa preležanim MI. LVEF-a ima značajan uticaj na benefit od fizičkog treninga, s tim što je benefit veći kod bolesnika bez RLVEF-a.

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***Ključne reči**: fizički trening, dvostruki proizvod, koronarna bolest, QT disperzija, ejekciona frakcija leve komore*

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PROF. DR SRĐAN PEŠIĆ (1963–2023), IN MEMORIAM

Prof. dr Srđan Pešić rođen je 28. 6. 1963. godine u Leskovcu, gde je završio osnovnu i srednju školu. Diplomirao je na Medicinskom fakultetu Univerziteta u Nišu 1988. godine i stekao zvanje doktora medicine.

Ubrzo nakon diplomiranja (1990. godine) izabran je za asistenta na Medicinskom fakultetu Univerziteta u Nišu na Katedri za farmakologiju sa toksikologijom, gde započinje njegova karijera jedinstvenog profesora. Na Medi-cinskom fakultetu Univerziteta u Nišu 1993. godine odbranio je magistarsku tezu pod naslovom „Analgetičko dejstvo inhibitora enkefalinaze N-karboksi-fenil leucina u pacova". Doktorsku disertaciju na temu „Uloga i značaj endotela u relaksaciji i kontrakciji humane interne mamilarne arterije" odbranio je na Medicinskom fakultetu Univerziteta u Beogradu 1998. godine. Zdravstvene specijalističke studije kliničke farmakologije završio je 2013. godine na Medicinskom fakultetu Univerziteta u Nišu. U zvanje redovnog profesora za užu naučnu oblast Farmakologija sa toksikologijom na Medicinskom fakultetu Univerziteta u Nišu izabran je 2012. godine i više godina bio odgovoran za rad Katedre za farmakologiju sa toksikologijom.

Obožavan od strane studenata, bio je predavač u okviru devet predmeta na Integrisanim akademskim studijama medicine, stomatologije i farmacije, kao i na osnovnim strukovnim studijama i doktorskim akademskim studijama i u nastavi lekara na specijalizacijama iz kliničke farmakologije, urgentne medicine i opšte medicine. Osim toga, bio je autor brojnih publikacija, pre svega udžbenika, priručnika i praktikuma, nastalih iz želje da studentima olakša savladavanje teorijskog znanja i praktičnih veština. Učestvujući u stvaranju podmlatka na Medicinskom fakultetu, prof. dr Srđan Pešić bio je mentor prilikom izrade brojnih diplomskih radova, magistarskih teza i doktorskih disertacija studenata medicine i farmacije. Bio je član specijalističkih komisija, član i predsednik komisija za izbor nastavnika i saradnika, kako na Medicinskom fakultetu u Nišu, tako i na drugim univerzitetima u Srbiji.

Prof. dr Srđan Pešić bio je član mnogobrojnih nacionalnih i internacionalnih stručnih udru-

ženja, kao što su *Physiological Society,* London, ACRP (*Association of Clinical Research Professionals*), EACPT (*The European Association for Clinical Pharmacology and Therapeutics*), *Srpsko farmakološko društvo, Srpsko fiziološko društvo, Društvo medicinskih mikologa Srbije, Sekcija za kliničku farmakologiju Srpskog lekarskog društva*. Njegov istraživački rad uslovio je da kao autor, koautor i nosilac istraživanja publikuje brojne naučne i stručne radove – od toga, 25 radova objavljeno je u prestižnim međunarodnim časopisima. Bio je učesnik pet naučnoistraživačkih projekata Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije. U okviru doktorskog usavršavanja boravio je na Institutu za farmakologiju, toksikologiju i kliničku farmakologiju Medicinskog fakulteta Univerziteta u Beogradu dve godine. Bio je recenzent i član uređivačkih odbora brojnih inostranih i domaćih naučnih časopisa, među kojima su *Canadian Journal of Pharmacology and Physiology*, *Indian Journal of Medical Sciences*, *DARU, the Journal of faculty of Pharmacy, Tehran University of Medical Sciences, Acta Medica Medianae* i *Acta Facultatis Medicae Naissensis*.

Njegov doprinos bio je često prepoznat, priznat i nagrađivan, te je postao dobitnik mnogih nagrada: nagrada *Srpskog lekarskog društva Podružnice Niš* za najbolju publikaciju u 2002. godini u kategoriji naučno-stručnih radova, nagrada Ministarstva za nauku i zaštitu čovekove okoline za najbolje istraživače u Srbiji za 2003/2004. godinu, *Srpskog lekarskog društva Podružnice Niš* za izuzetan doprinos razvoju medicinske nauke i struke i nagrada dodeljna od strane njegovog voljenog Leskovca, *Medalja Skupštine grada Leskovca* za naučni doprinos u oblasti kliničke farmakologije i doprinos afirmaciji grada Leskovca.

Profesor i kolega dr Srđan Pešić bio je čovek od integriteta, spreman da pomogne svima. Krasili su ga intelektualno poštenje, posvećen rad i beskrajno šarmantna prezentacija svega. Dobar otac, dobar suprug, dobar prijatelj, dobar professor, dobar stručnjak, dobar edukator, pun ideja, bio je omiljen od strane svojih studenata, doktoranada, specijalizanata, kao i prijatelja i kolega širom naše zemlje.

Profesori i saradnici Katedre za farmakologiju

Srđan Pešić bio je sjajan student, zatim doktor, farmakolog i istraživač i nezaboravan predavač, profesor i prijatelj. Uz vanredan šarm, naš Peki bio je jedan od najvećih boraca protiv nepravde, neznanja i tuge. Otkad je otišao, ja više nemam s kim da ispravljam „krive Drine", kojih je tako mnogo na ovom svetu.

Prof. Suzana Otašević

Čovek je svestan smrti upravo zato što je umno biće. Taj vlastiti bolni uvid, koji uništava radost življenja i koji bi mogao da parališe volju za životom kod svake individue, nije se desio kod našeg druga, profesora Srđana Pešića Pekija. Naš profesor Srđan Pešić imao je izuzetne ljudske osobine; bio je tolerantan, nesebičan, iskren, osećajan, razumeo je probleme drugih ljudi i, možda najvažnije, bio je čovek od integriteta. U današnjem svetu, biti dobra osoba, kakav je bio naš veliki profesor Pešić, nije lako i predstavlja pravi životni poduhvat. Njegova dobrota je bila istinita i dolazila je iz srca. Radio je predano – tako je želeo, tako je odlučio jer ga je to ispunjavalo. Davao je primer ponašanja dobrog čoveka. Kada je neko tolerantan i dobar kao što je bio naš Peki, to ne znači da je bio sa svime što se dešava oko njega hladan i opušten, već znači da je naučio da bude trpeljiv, da može da podnese vrlo neprijatne stvari, a da ipak ostane svoj. Biti dobra osoba je za profesora Srđana Pešića bio smisao života.

Prava ljubav prema porodici, roditeljima, svojoj deci i pravim prijateljima jeste onda kada ih volimo, a ne očekujemo da se ikada promene.

TAKAV JE BIO I OSTAO NAŠ DRUG SRĐAN PEŠIĆ, REDOVNI PROFESOR FARMAKOLOGIJE SA TOKSIKOLOGIJOM NA MEDICINSKOM FAKULTETU U NIŠU.

Prof. dr Nikola Burić

Veliki ljudi ne umiru, oni i dalje žive u našim srcima, dušama i mislima. Srđan Pešić je bio najbolji među nama, najbolji drug i prijatelj, najbolji profesor, natprosečno inteligentan čovek, avanturista, liberal; voleo je život, voleo je slobodu i bio je svoj!

Hvala mu za privilegiju koju je svima nama pružio – poznavali smo ga i mogli smo se pohvaliti da smo njegovi drugovi!

Prof. dr Dušan Sokolović

Tako malo ljudi na ovoj kugli zemaljskoj ima privilegiju da živi slobodno, da taj put izabere za sebe bez obzira na to što je teži, duži i mukotrpniji. Još je manje onih koji za života zasluže da budu zanavek upamćeni, poštovani i voljeni. Živeli smo život ushićeni, srećni i ne tako retko uzbuđeni

svakim novim nadolezećim danom, svakim novim životnim projektom, pričali o Ljosi, divili se Andima i beskraju Patagonije. Od studentskih dana kada si mi bio mentor, preko burnih devedesetih kada si mi bio saborac, do ranih dvehiljaditih kada si mi bio lični, životni i porodični oslonac... Srđan Pešić je bio erudita, hrabar slobodnoumni čovek, dosledan principima i veran pravdi. Bio je svoj, bio je jedinstven. Jednostavno, bio je najbolji od nas. Putuj, prijatelju, naći ćemo se opet mi, na nekim novim vrhovima...

Prof. dr Radmilo Janković

PROPOZICIJE ZA PISANJE RADOVA U ACTA MEDICA MEDIANAE

Acta Medica Medianae (AMM) je tematski časopis iz oblasti medicinskih nauka. Časopis objavljuje originalne radove koji nisu prethodno publikovani.

U AMM se objavljuju: uvodnici, naučni i stručni članci, prethodna ili kratka saopštenja, revijski radovi tipa opšteg pregleda, aktuelne teme, meta-analize, prikazi slučajeva, prikazi knjiga i drugi prilozi. Radovi se štampaju na srpskom ili engleskom jeziku sa apstrak-tom na srpskom i engleskom jeziku. Radovi na engles-kom jeziku se prezentuju u elektronskom formatu na sajtu Medicinskog fakulteta u Nišu, kao i na među-narodnim sajtovima iz oblasti medicinskih nauka. Acta Medica Medianae izlazi četiri puta godišnje, od 1962 godine.

Svi radovi koji se objavljuju u AMM podležu anonimnoj recenziji, a Uređivački odbor određuje redosled njihovog štampanja. Primedbe i sugestije urednika i recenzenata dostavljaju se autoru radi konačnog oblikovanja. Radovi se predaju u pisanom ili elektronskom obliku na srpskom i engleskom jeziku. Rukopisi radova prihvaćenih za štampu ne vraćaju se autoru.

Rukopis treba predati sa jednostrukim proredom, formata A4, sa levom marginom od 3 cm.

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