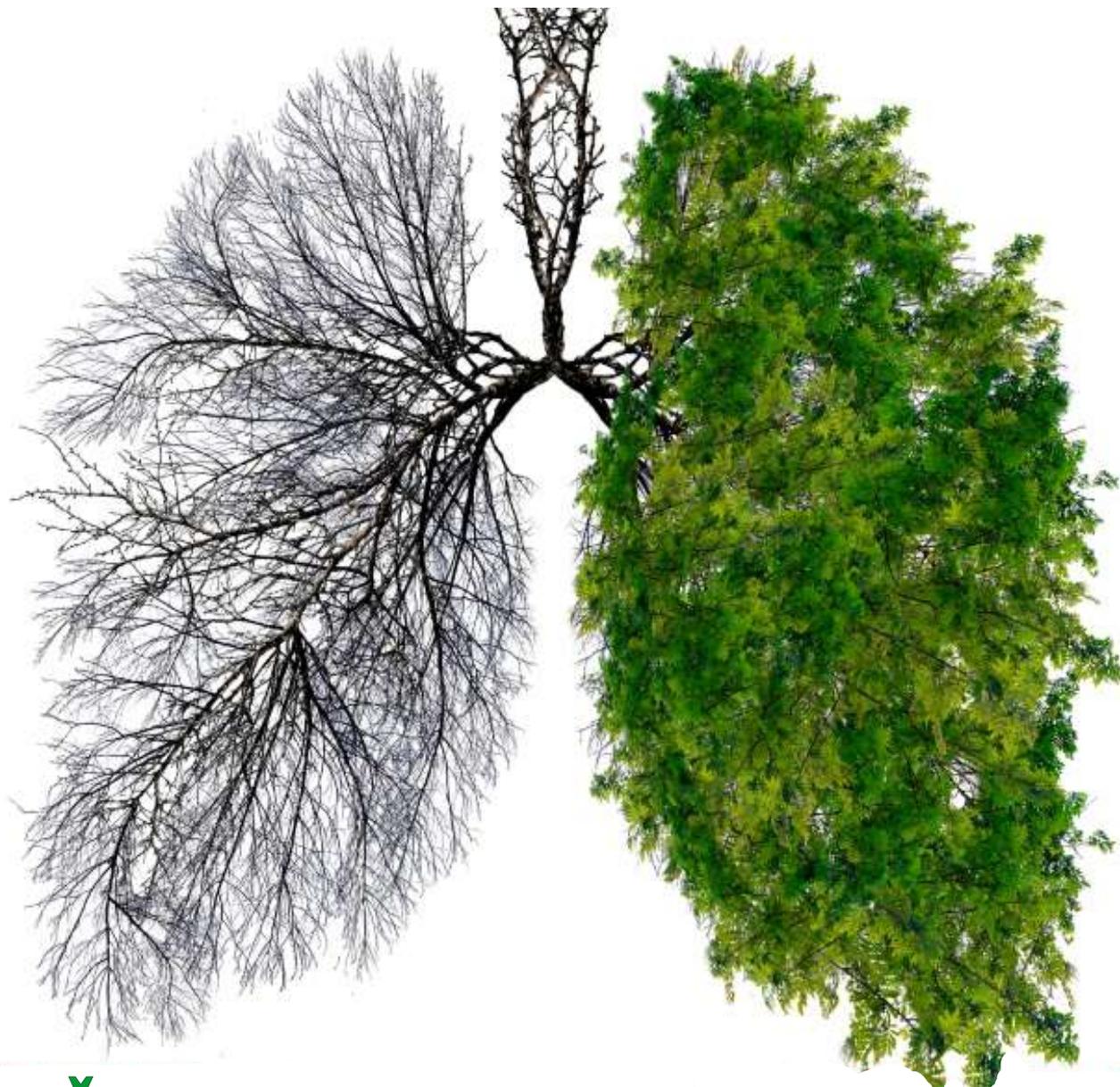


# MEDICAL JOURNAL MEDICINSKI ŽURNAL

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## Novi Evropski vodič za prevenciju tromboembolizma kod A Fib CHA<sub>2</sub>DS<sub>2</sub>-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

Risk factor-based point-based scoring system - CHA <sub>2</sub> DS <sub>2</sub> -VASc	
Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65–74	1
Sex category (i.e. female sex)	1
<b>Maximum score</b>	<b>9</b>

\*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.



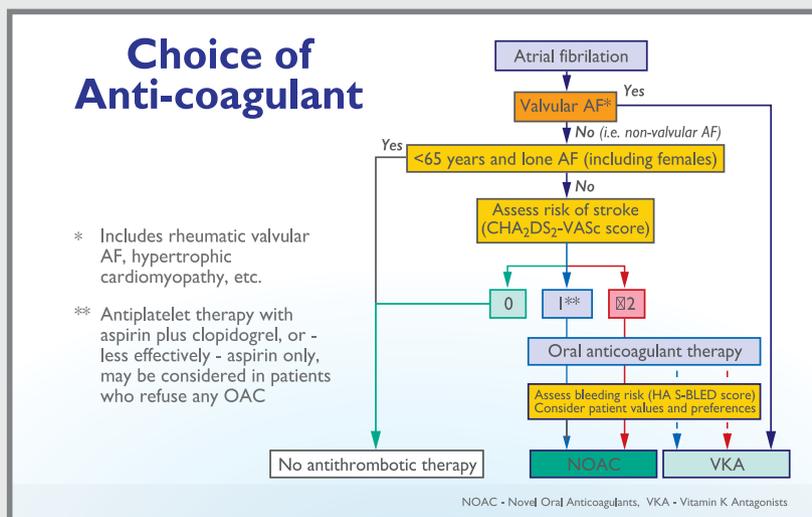
## Major i non-major riziko faktori za procjenu tromboembolizma kod A Fib!

Risk factors for stroke and thrombo-embolism in non-valvular AF	
Major risk factors	Clinically relevant non-major risk factors
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TIA or systemic embolism	Hypertension
Age ≥75 years	Diabetes mellitus
	Age 65-74 years
	Female sex
	Vascular disease

AF = atrial fibrillation; EF = ejection fraction (as documented by echocardiography, radio nuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.



## Algoritam antikoagulantne terapije nakon procjene CHA<sub>2</sub>DS<sub>2</sub>VASc i major risk faktora!



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# The efficacy of intra-umbilical vein administration of carboprost versus oxytocin in the management of retained placenta: surgical and non-surgical risk factors

## Efikasnost intra-umbilikalne venske aplikacije karboprosta i oksitocina u tretmanu zaostale posteljice: hirurški i nehirurški faktori rizika

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### ABSTRACT

**Introduction:** retained placenta is one of the major causes of primary and secondary post-partum hemorrhage (PPH) and active management of the third stage of labor reduces the risk of PPH. **Aim:** to compare the efficacy of intra-umbilical vein injection of carboprost versus oxytocin by different medication doses and surgical and non-surgical risk factors in the management of retained placenta. **Materials and methods:** this prospective clinical study was conducted at the Clinic of Obstetrics and Gynecology of the Clinical Center University of Sarajevo, in the two-year period. Patients were randomized in 4 groups and 8 subgroups, respectively: A<sub>1</sub>(n=25) (carboprost, surgical risk factors, 1 amp. a 0.5 mg in 30 ml of 0.9%NaCl); A<sub>2</sub>(n=25) (carboprost, surgical risk factors, 1 amp. a 1.0 mg in 30 ml of 0.9%NaCl); B<sub>1</sub>(n=25) (oksytocin, surgical risk-factors, 10 UI in 20 ml of 0.9% NaCl); B<sub>2</sub>(n=25)(oksytocin, surgical risk-factors, 20 UI in 20 ml of 0.9% NaCl); C<sub>1</sub>(n=25) (carboprost, non-surgical risk factors, 1 amp. a 0.5 mg in 30 ml of 0.9%NaCl); C<sub>2</sub>(n=25) (carboprost, non-surgical risk factors, 1 amp. a 1.0 mg in 30 ml of 0.9%NaC l); D<sub>1</sub>(n=25) (oksytocin, non-surgical risk-factors, 10 UI in 20 ml of 0.9% NaCl); D<sub>2</sub>(n=25) (oksytocin, non-surgical risk-factors, 20 UI in 20 ml of 0.9% NaCl). The main outcome variable was expulsion of retained placenta and second outcome variables were: duration of time from intra-umbilical vein administration of drug to expulsion of retained placenta, the number of cases who required blood transfusion and antibiotics, postpartum hemoglobin after 24h. **Results:** the group B<sub>2</sub> (UVI oxytocin 20 IU in 20 mL saline, surgical risk factors) and the group D2 (UVI oxytocin 20 IU in 20 mL saline, non-surgical risk factors) had shorter expulsion time (minutes) (Me=5; IQR=4 to 5; Me=5; IQR=4.3 to 6, respectively) compared with other groups (p<0.001). The success rates of total expulsion of the placenta by groups were not statistically significant (70% vs. 82% vs. 72% vs. 78%, respectively; p=0.483). Post-intervention hemoglobin concentrations was statistically significantly greater in the group B (117.3±1.3) vs. the group A (112.1±1.3), (p =0.028). **Conclusion:** there is no difference in the rates of the total expulsion of the placenta comparing IUV

injection of carboprost versus oxytocin in the management of retained placenta. The time for placental expulsion was significantly shorter and postpartum hemoglobin (117.3±1.3) was significantly higher in the intra-umbilical oxytocin groups than in the carboprost groups.

**Keywords:** retained placenta, oxytocin, carboprost, placental expulsion

### SAŽETAK

**Uvod:** zaostala posteljica predstavlja jedan od glavnih uzroka primarne i sekundarne postpartalne hemoragije (PPH), te aktivno vođenje trećeg porođajnog doba smanjuje rizik od PPH. **Cilj:** uporediti efikasnost intra-umbilikalne venske aplikacije karboprosta i oksitocina prema vremenu i učestalosti ekspanzije posteljice. **Materijali i metode:** sprovedena je prospektivna klinička studija na Klinici za ginekologiju i porodiljstvo Kliničkog centra Univerziteta u Sarajevu u 2-godišnjem periodu. Ispitanice su randomizirane u 4 grupe, odnosno 8 podgrupa: A<sub>1</sub>(n=25) (karboprost, hirurški faktori rizika, otopina 1 amp. a 0,5 mg karboprosta u 30 ml 0,9%NaCl); A<sub>2</sub>(n=25) (karboprost, hirurški faktori rizika, otopina 1 amp. a 1,0 mg karboprosta u 30 ml 0,9%NaCl); B<sub>1</sub>(n=25) (oksitocin, hirurški faktori rizika, otopina 10 UI u 20 ml 0,9% NaCl); B<sub>2</sub>(n=25) (oksitocin, hirurški faktori rizika, otopina 20 UI u 20 ml 0,9% NaCl); C<sub>1</sub>(n=25) (karboprost, nehirurški faktori rizika, otopina 1 amp. a 0,5 mg karboprosta u 30 ml 0,9%NaCl); C<sub>2</sub>(n=25) (karboprost, nehirurški faktori rizika, otopina 1 amp. a 1,0 mg karboprosta u 30 ml 0,9%NaCl); D<sub>1</sub>(n=25) (oksitocin, nehirurški faktori rizika, otopina 10 UI u 20 ml 0,9% NaCl); D<sub>2</sub>(n=25) (oksitocin, nehirurški faktori rizika, otopina 20 UI u 20 ml 0,9% NaCl). **Glavna mjera ishoda** je bila ekspanzija zaostale posteljice, te su praćene i zamjenske mjere ishoda: vrijeme od intra-umbilikalne venske aplikacije lijeka do ekspanzije posteljice, učestalost transfuzije krvi i aplikacije antibiotika, postpartalna vrijednost hemoglobin nakon 24h. **Rezultati:** grupa B2 (intra-umbilikalna venska aplikacija oksitocina 20 i.j.u 20 ml 0,9% fiziološke otopine, hirurški riziko-faktori) i grupa D2

(intra-umbilikalna venska aplikacija oksitocina 20 i.j.u 20 ml 0,9% fiziološke otopine, nehirurški riziko-faktori) su imali kraće vrijeme ekspanzije posteljice (minute) (Me=5, IQR=4 to 5; Me=5, IQR=4,3 to 6, zaredom) u poređenju sa ostalim grupama ( $p<0,001$ ). Ne postoji statistički značajna razlika u stopi uspjehnosti totalne ekspanzije zaostale posteljice među grupama: A, B, C i D (70%, 82% 72%, 78%, zaredom;  $p=0,483$ ). Post - intervencijski nivo hemoglobina je bio statistički značajno veći u grupi B ( $117,3\pm1,3$ ) u poređenju sa grupom

A ( $112,1\pm1,3$ ), ( $p=0,028$ ). Zaključak: vrijeme ekspanzije zaostale posteljice je signifikantno kraće, dok su postpartalne vrijednosti hemoglobina ( $117,3\pm1,3$ ) znatno više kod intra-umbilikalne venske aplikacije oksitocina u poređenju sa karboprostom, pri aktivnom tretmanu zaostale posteljice.

**Ključne riječi:** zaostala posteljica, oksitocin, karboprost, ekspanzija posteljice

## INTRODUCTION

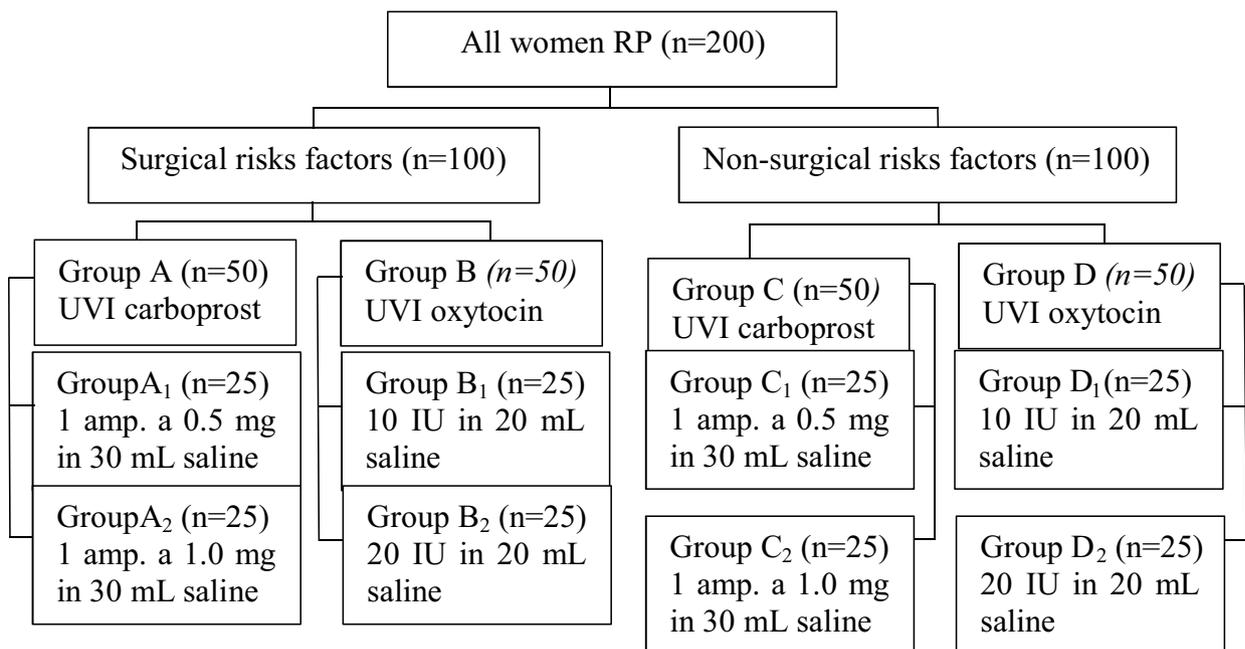
Retained placenta is one of the major causes of primary and secondary post-partum hemorrhage (PPH), associated with increased risk of maternal morbidity and mortality (1). PPH accounts for nearly one quarter of all maternal deaths world-wide with an estimated 125,000 deaths per year (2). One of the main causes of PPH is retained placenta, which affects 0.5% to 3.0% of women following delivery, and a further 15% to 20% of the PPH maternal deaths are due to retained placenta (3,4). There are three main types of retained placenta following the vagina delivery: placenta adherens (when there is failed contraction of the myometrium behind the placenta), trapped placenta (a detached placenta trapped behind a closed cervix) and partial accreta (when there is a small area of accreta preventing detachment) (5,6). Risk factors that can lead to retained placenta can be divided into surgical and non-surgical risk factors (7,8,9,10). Surgical risk factors are: the number of cesarean sections, the number of spontaneous abortions and their gestational age, the number of artificial abortions and gestational age, the number of uterine cavity abrasions, hysterosalpingography (HSG), hysteroscopy (diagnostic and operative), myomectomy, Sy Asherman (surgical etiology). Non-surgical risk factors are: congenital anomalies of the uterus, endometrial synechiae (Sy Asherman) of inflammatory etiology, amniocentesis syndrome, untreated endometritis, pluripara (more than 3 births), placenta membranacea (large placenta), usage

of tocolytics in current pregnancy. The term 'retained placenta' is used when the placenta has not been delivered within one hour after the birth of the baby (11). The length of the third stage of labor is a potential modifiable risk factor for PPH at vaginal delivery, but there is no definitive evidence that early intervention to remove the placenta manually will prevent PPH.

The usage of uterotonic agent in the management of retained placenta is under debate. This study aimed to compare the efficacy of intra - umbilical vein injection of carboprost versus oxytocin by different medication doses and surgical and non-surgical risk factors in the management of retained placenta.

## MATERIALS AND METHODS

This prospective clinical study was conducted at the Clinic of Obstetrics and Gynecology, Clinical Center of University of Sarajevo in the two-year period and included 200 patients. Informed consent was obtained in all cases and risk factors were identified, via a questionnaire, additionally. We studied all the patients prospectively and by computerized randomization. All patients underwent a gynecological sonography with Voluson E6 Ultrasound General Electric (EG), upon admission to the Clinic. Patients were randomized in 2 groups by surgical risks factors (Table 1 and Table 2) and 8 subgroups by medication and doses.



**Flowchart for the study** Abbreviations: *RP*retained placenta, *UVI*umbilical vein injection, *IU*international unit

The exclusion criteria were uterine atony and bleeding > 500 ml; maternal hemodynamic instability (pulse  $\geq$  120 b.p.m., or a decrease in diastolic blood pressure of more than 20mm Hg after delivery, associated medical disorders (e.g., cardiac disease, anemia, hypertension and diabetes), multiple pregnancy. The main outcome variable was expulsion of retained placenta and second outcome variables were: duration of time from intra-umbilical vein administration of drug to expulsion of RP, the number of cases who required blood transfusion and antibiotics, postpartum hemoglobin after 24h.

The included women were with a singleton living fetus, achieved vaginal delivery, and failed to deliver the placenta after 30 minutes of active management of the third stage of labor (intravenous administration of 5 IU of Syntocinon in the presence of an intact umbilical cord, fundal pressure and controlled cord traction after 5, 10 and 15 minutes) in all patients. A retained placenta was diagnosed when separation did not occur 30 minutes after delivery and UVI is followed. The appropriate solution was injected into the umbilical vein for 15 seconds by type of treatment and the umbilical cord was clamped again. At 5 and 10 minutes after administration of the medication, or in the case of clinical signs of placental separation, an attempt to deliver the placenta was made. If the final attempt to deliver the placenta failed, manual removal was performed by the usual maneuver under general anesthesia. Standard management of the third stage of labor was continued, including blood transfusion and uterotonic agents for continued bleeding. Evaluation of the drop in hemoglobin level was done by comparing the hemoglobin concentration on admission and 24h after delivery.

### Statistical analysis

The results are presented as the means and standard deviations ( $\pm$ SD) for numerical variables and as numbers and percentages for categorical variables. Statistical significance for differences was analyzed using the One-Way ANOVA, One-Way ANCOVA, Kruskal Wallis H test. Post-hoc analysis was performed using Independent Sample T test or Mann Whitney U test with Bonferroni correction for multiple testing. Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS Release 19.0; SPSS Inc., Chicago, Illinois, United States of America) software. Statistical significance was accepted for p-values < 0.05.

## RESULTS

The frequency of surgical and non - surgical risk factors by groups is shown in Tables 1 and 2.

Table 1 The frequency of surgical risk factors by groups.

Surgical risk factors	Group A (n=50)		Group B (n=50)	
	n	%	n	%
C - sections	5	10.0	5	10.0
Premature birth	8	16.0	2	4.0
Stillbirth	2	4.0	1	2.0
Exploration	18	36.0	19	38.0
Artificial abortion				
0	38	76.0	18	36.0
1	5	10.0	9	18.0
2	6	12.0	18	36.0
3	1	2.0	5	10.0
Spontaneous abortion				
0	22	44.0	20	40.0
1	5	10.0	6	12.0
2	18	36.0	17	34.0
3	5	10.0	7	14.0
Myomectomy	6	12.0	7	14.0
Hysteroscopy	13	26.0	15	30.0

Table 2 The frequency of non - surgical risk factors by groups.

Non – surgical factors	Group C (n=50)		Group D (n=50)	
	n	%	n	%
Intrauterine adhesions (IUAs)	6	12,0	7	14,0
Pluriparous (>3 births)	5	10,0	6	12,0
Placenta membranacea/diffusa	8	16,0	11	22,0
Tocolytics	31	62,0	26	52,0

The demographic and obstetric data of the study groups were comparable, except for the level of education (p<0.05) and term or preterm delivery (p<0.01) (Table 3).

Table 3 Demographic and clinical characteristics.

	Surgical risk factors				Non – surgical risk factors				P-value
	Group A (n=50) UVI carboprost		Group B (n=50) UVI oxytocin		Group C (n=50) UVI carboprost		Group D (n=50) UVI oxytocin		
<i>Maternal age (y)<sup>a</sup></i>	27.7±3.7		26.5±4.7		28.7±5.2		26.2±5.4		>0.05
<i>Gestational age (weeks)<sup>a</sup></i>	38.4±3.1		39.0±1.0		38.8±1.4		39.0±1.0		>0.05
<i>Birth length (cm)<sup>c</sup></i>	52.0 (50 to 53)		52.0 (51 to 53)		52.0 (52 to 53)		51.0 (50 to 53)		>0.05
<i>Birth weight (grams)<sup>c</sup></i>	3400 (3000 to 3825)		3500 (3175 to 3.862)		3425 (2987 to 3912)		3700 (3200 to 3950)		>0.05
<i>Level of education<sup>b</sup></i>									
Elementary school	4	8.0	3	6.0	6	12.0	6	12.0	0.037
High school	43	86.0	38	76.0	33	66.0	29	58.0	
Higher education	3	6.0	9	18.0	11	22.0	15	30.0	
<i>Delivery<sup>b</sup></i>									
Term	43	86.0	50	100.0	46	92.0	50	100.0	0.001
Preterm	7	14.0	0	0.0	4	8.0	0	0.0	
<i>Smoking<sup>b</sup></i>									
No	35	70.0	32	64.0	33	66.0	35	70.0	>0.05
Yes	15	30.0	18	36.0	17	34.0	15	30.0	
<i>Smoking duration (y)<sup>a</sup></i>	4.9±1.6		4.3±1.9		4.9±1.5		4.7±1.9		>0.05

Data are presented as: <sup>a</sup> mean±SD, <sup>b</sup> number or percentage (%), <sup>c</sup> median (IQR)

The results for the main and secondary outcomes and the success rate are presented in Table 4. The time for placental expulsion was significantly shorter in the intra-umbilical oxytocin groups than in the carboprost groups ( $p < 0.001$ ). The post hoc analysis revealed statistically significant differences in the time for placental expulsion (minutes) between the groups B<sub>2</sub> (Me=5; IQR=4 to 5) and D<sub>2</sub> (Me=5; IQR=4.3 to 6) compared with groups: A<sub>1</sub> (Me=9; IQR=8 to 9) ( $p < 0.001$ ), A<sub>2</sub> (Me=8; IQR=6.3 to 9) ( $p < 0.001$ ), B<sub>1</sub> (Me=7; IQR=6.3 to 8) ( $p < 0.001$ ), C<sub>1</sub> (Me=8.5; IQR=8 to 9) ( $p < 0.001$ ), C<sub>2</sub> (Me=7; IQR=6.5 to 9) ( $p < 0.001$ ) and D<sub>1</sub> (Me=7; IQR=5.8 to 9) ( $p < 0.001$ ), but not between the B<sub>2</sub> and D<sub>2</sub> groups or any other group combination (Figure 1).

Table 4 The outcome of the third stage of labor.

	Surgical risk factors				Non – surgical risk factors				P-value
	Group A (n=50) UVI carboprost		Group B (n=50) UVI oxytocin		Group C (n=50) UVI carboprost		Group D (n=50) UVI oxytocin		
<i>Placental expulsion (min)<sup>a</sup> (years)<sup>a</sup></i>	8.5 (7.0 to 9.0)		6.0 (4.9 to 7.0)		8.0 (6.5 to 9.0)		6.0 (4.5 to 8.0)		<0.001
<i>Placenta expelled spontaneously<sup>b</sup></i>	35	70.0	41	82.0	36	72.0	39	78.0	>0.05
<i>Manual removal of placenta<sup>b</sup></i>	15	30.0	9	18.0	14	28.0	11	22.0	>0.05
<i>Secondary postpartum hemorrhage<sup>b</sup></i>	0	0.0	0	0.0	0	0.0	0	0.0	-
<i>Blood transfusion<sup>b</sup></i>	4	8.0	2	4.0	8	16.0	3	6.0	>0.05
<i>Antibiotics<sup>b</sup></i>	18	36.0	16	32.0	38	76.0	17	34.0	<0.001
<i>Success rate (%)</i>	70.0		82.0		72.0		78.0		>0.05

Data are presented as: <sup>a</sup> median (IQR), <sup>b</sup> number or percentage (%)

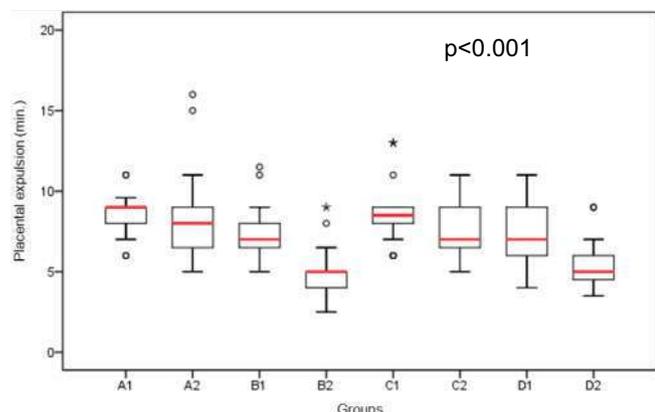


Figure 1 Time for placental expulsion (min.) by different groups in the study. Data are presented as median (IQR).

There was no statistically significant difference between A, B, C and D groups and subgroups in the success rates of the total expulsion of placenta (70% vs. 82% vs. 72% vs. 78%, respectively,  $p=0.483$ ). The frequency of blood transfusion was not statistically different between the four groups (Table 4). Of the total number of patients in group A ( $n=50$ ), 4 (8.0%) of them had a blood transfusion ( $M=525 \pm 150$  ml), in group B ( $n=50$ ) only 2 (4.0%) patients had a blood transfusion ( $M=300$  ml), in group C ( $n=50$ ) 8 (16%) patients had a blood transfusion ( $M=375 \pm 70$  ml) and in group D ( $n=50$ ) 3 (6.0%) patients had a blood transfusion ( $M=300$  ml).

Table 5 Adjusted and unadjusted means and variability for 24h post-partum hemoglobin concentration (g/L) with pre-intervention hemoglobin concentration as a covariate.

Groups	Adjusted means		Unadjusted means		$F_{3,195}$	$p$	$\eta^2_p$
	M	SE	M	SE			
A	110.2	1.1	112.1	1.3	3.08	0.02	0.04
B	118.2	1.0	117.3	1.3			
C	115.8	1.2	114.7	1.3			
D	116.1	1.1	116.2	1.3			

M – mean; SE – standard error; F – value of test;  $\eta^2_p$  – effect size

After adjustment for pre-intervention hemoglobin concentration, there was a statistically significant difference in post-intervention hemoglobin concentrations between the interventions.  $F(3, 195) = 3.081$ ,  $p = 0.029$ , partial  $\eta^2 = 0.045$ . Post-intervention hemoglobin concentrations was statistically significantly greater in the group B ( $117.3 \pm 1.3$ ) vs. the group A ( $112.1 \pm 1.3$ ), ( $p = 0.028$ ). After adjustment for pre-intervention hemoglobin concentration, there was not a statistically significant difference in post-intervention hemoglobin concentrations between subgroups.

## DISCUSSION

In this study we compared efficacy of the intra-umbilical vein administration carboprost versus oxytocin in the management of retained placenta by surgical and non-surgical risk factors and different doses of medication. Oxytocin is the most commonly used uterotonic and has been well known in midwifery for a long time

(12). In placenta adherens, oxytocics have been used to contract the retro-lacental myometrium. However, if injected locally through the umbilical vein, they bypass the myometrium and perfuse directly into the venous system (13). In the randomized clinical study of Elfayomy AK., the success rate in the carboprost group was 86.84% compared to 77.5% in the intra-umbilical oxytocin group (14). In the study of Habek D, et al., there were no statistically significant differences among groups: 20 IU of oxytocin in 20 ml saline; 0.5 mg of carboprost tromethamine; or 0.2 mg of methylergometrine injected in the umbilical vein after clamping (76.9% vs.85.7% vs.64.2% (15). We did not find a significant difference in the rates of the total expulsion of the placenta comparing IUV injection of carboprost versus oxytocin in the management of retained placenta by using different doses of medications. In our study, the subgroups that received oxytocin 20 IU in 20 ml saline, with both surgical and non-surgical risk factors, had the highest frequency of placental expulsion (80-88%) compared to the groups that received carboprost with doses 0.5 mg or 1.0 mg in 30 ml saline (68- 76%). However, the difference did not reach the level of statistical significance.

In the study of Nankali A, et al., the women who received intraumbilical vein oxytocin had a shorter third stage of labor as compared with the placebo group ( $4.24 \pm 3.27$  min vs.  $10.66 \pm 7.41$ ) ( $p < 0.001$ ) (16). The present study showed a statistically significant reduction in the median of duration of third stage of labor in the group B<sub>2</sub> (UVI oxytocin 20 IU in 20 mL saline, surgical risk factors) and the group D2 (UVI oxytocin 20 IU in 20 mL saline, non-surgical risk factors) (Me=5; IQR=4 to 5; Me=5; IQR=4.3 to 6, respectively) compared with other groups. The present study did not demonstrate any differences between the groups in the amount of blood transfusion. Hemoglobin concentration 24h after delivery was lower in carboprost group than in the oxytocin group for surgical risk factors. Five women required blood transfusion in oxytocin group for excessive bleeding and twelve women in carboprost group. This indicates positive effect of oxytocin in reducing bleeding complications.

The time until manual removal of placenta in the absence of bleeding varies widely between different countries, from under 30 minutes (Spain and Hungary) to 60 minutes and more (The Netherlands) (17). In the study of Cummings K et al., the optimal length of the third stage of labor to prevent PPH was 18min (18). In the study of over 12,000 births, Combs and Laros found that the risk of hemorrhage increased after 30 minutes of placental retention (19). Active management of the third stage of labor involves administration of intravenous oxytocin, early cord clamping, transabdominal manual massage of the uterus, and controlled traction of the umbilical cord. Should this appear insufficient, the next step is usually manual removal of the placenta (20). In the guidelines of Leduc D. et al., it is concluded that active management of the third stage of labor reduces the risk of PPH and should be offered and recommended to all women (21).

A limitation of our study is that it is done at single center, thus, results may not be applicable to other populations.

## CONCLUSION

There is no difference in the rates of the total expulsion of the placenta comparing IUV injection of carboprost versus oxytocin in the management of retained placenta. The time for placental expulsion was significantly shorter and postpartum hemoglobin was significantly higher in the intra-umbilical oxytocin groups than in the carboprost groups.

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# Vitamin D deficiency and hypothyroidism in individuals with Down syndrome

## Nedostatak vitamina D i hipotireoza kod osoba sa Downovim sindromom

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### ABSTRACT

Introduction: vitamin D deficiency is a global health problem and leads to serious problems. Hypothyroidism is a condition in which the thyroid gland is not able to produce enough thyroid hormone. Aim: to investigate the prevalence of Hypothyroidism and vitamin D deficiency in patients affected with Trisomy 21. Materials and methods: this is a retrospective study conducted in the three-year period, specifically from 1 May 2019 to 31 April 2021, and it included 60 respondents with Down syndrome whose blood samples were collected and analysed at the Clinical Center University of Sarajevo. Data collected included laboratory reports such as profiles of both D vitamin and thyroid hormones. Laboratory tests were performed at the Institute of Clinical Chemistry and Biochemistry of the Clinical Center University of Sarajevo using standard determination methods. Results: out of the total of 60 examined patients tested for vitamin D and TSH levels, females were in majority with 60% and males with 40%. Differences in Vitamin D values between intervals (1-4 Check-up) with Kruskal Wallis test showed a statistically significant difference in values of Vitamin D (ng/mL) between check-ups, with  $p < 0.001$ . Differences in TSH values between intervals (1-4 check-up) with Kruskal Wallis test showed a statistically significant difference in values of TSH (uIU/mL) between check-ups, with  $p < 0.001$ . Correlation between Vitamin D (ng/mL) and TSH values (uIU/mL) with Spearman's correlation between TSH and Vitamin D showed a statistically significant negative correlation between the two, with  $p < 0.001$ . Conclusion: the research showed the occurrence of hypothyroidism and vitamin D deficiency in subjects with Dawn syndrome.

**Keywords:** vitamin D, hypothyroidism, Down syndrome

### SAŽETAK

Uvod: nedostatak vitamina D je globalni zdravstveni problem koji dovodi do ozbiljnih problema. Hipotireoza je stanje u kojem štitna žlijezda nije u stanju proizvesti dovoljno hormona. Cilj: istražiti prevalenciju hipotireoze i nedostatka vitamina D kod bolesnika s trisomijom 21. Materijali i metode: ovo je retrospektivna studija provedena u trogodišnjem periodu, od 1. maja 2019. do 31. aprila 2021. godine, koja je obuhvatila 60 ispitanika s Downovim sindromom čiji su uzorci krvi prikupljeni i analizirani na Kliničkom centru Univerziteta u Sarajevu. Prikupljeni podaci uključivali su laboratorijske nalaze koji su se odnosili na vrijednosti vitamina D i hormona štitne žlijezde. Laboratorijska ispitivanja obavljena su na Institutu za kliničku hemiju i biohemiju Kliničkog centra Univerziteta u Sarajevu standardnim metodama određivanja. Rezultati: od ukupno 60 pregledanih pacijenata kojima je testiran nivo vitamina D i TSH, najviše je bilo žena sa 60%, a muškaraca sa 40%. Razlike u vrijednostima vitamina D između intervala (1-4 kontrole) Kruskal Wallis testom pokazale su statistički značajnu razliku u vrijednostima vitamina D (ng/mL) između kontrola, sa  $p < 0,001$ . Razlike u vrijednostima TSH između intervala (1-4 kontrole) Kruskal Wallis testom pokazale su statistički značajnu razliku u vrijednostima TSH (uIU/mL) između kontrola, sa  $p < 0,001$ . Korelacija između vrijednosti vitamina D (ng/mL) i TSH (uIU/mL) sa Spearmanovom korelacijom između TSH i vitamina D pokazala je statistički značajnu negativnu korelaciju između te dvije vrijednosti,  $p < 0,001$ . Zaključak: istraživanje je pokazalo pojavu hipotireoze i nedostatka vitamina D kod ispitanika s Dawnovim sindromom.

**Ključne riječi:** vitamin D, hipotireoza, Downov sindrom

### INTRODUCTION

Vitamin D deficiency is a global health problem (1) and leads to serious problems, can result in low bone mass (2). The effects of vitamin D independent of calcium, magnesium, and Vitamin D

deficiency plays a significant role in a dozens of numerous disorders (3).

Hypothyroidism is a condition in which the thyroid gland produces less thyroid hormone than it should. TSH normal values are 0.3-4.2 mIU/L. High TSH levels indicate that the thyroid is underactive and that it needs more stimulation in order to work. The

thyroid gland produces two hormones: triiodothyronine (T3) and thyroxine (T4). These hormones play an important role in metabolism. The thyroid gland is controlled (regulated) by thyroid-stimulating hormone (TSH). TSH is produced by the pituitary gland, which is located in the brain. When the thyroid gland produces less thyroid hormone than it should (hypothyroidism), metabolism slows down and causes a variety of symptoms (4,5). The main test used to detect hypothyroidism is measuring blood levels of TSH.

Down syndrome (DS), or trisomy of chromosome 21, is the most common genetic disorder when a child is born with an extra copy of chromosome (6).

## AIM

The aim of this study was to investigate the prevalence of Hypothyroidism and vitamin D deficiency in patients affected with Trisomy 21.

## MATERIALS AND METHODS

This is a retrospective study conducted in the three-year period, specifically from 1 May 2019 to 31 April 2021, and it included 60 respondents with Down syndrome whose blood samples were collected and analysed at the Clinical Center University of Sarajevo. Data collected included laboratory reports such as profiles of both D vitamin and thyroid hormones. Total of with 60 samples were taken and analysed. Laboratory tests were performed at the Institute of Clinical Chemistry and Biochemistry of the Clinical Center of the University of Sarajevo using standard determination methods.

Elecsys Vitamin D total is used for calibrating the quantitative Elecsys Vitamin D total assay reagents on the Elecsys and cobas e immunoassay analyzers. Serum 25(OH) vitamin D in human serum matrix and Thyroid hormone values were measured using Rosche Elecsys system on Cobas e 6000 analyzers by ECLIA method.

D vitamin and TSH were measured at the beginning of the study and after 3, 6, 9 and 12 months. Referral values for using this method D vitamin ranges are 30.0-100.0 ng/mL. Normal TSH value is (0.3-4.2 mIU/l).

### Statistical analysis

Data were analysed using MS Office Excel 2016 and SPSS Statistics 21.0, by descriptive and inferential statistical methods. Numeric variables were described by appropriate measures of central tendency and variability (mean/median and standard deviation/interquartile range, normality tested using Kolmogorov-Smirnov and Shapiro-Wilk tests), while qualitative variables were described using absolute and relative frequencies. Null hypotheses were tested with appropriate statistical tests (Mann-Whitney, Kruskal-Wallis). Results were also presented in tables and graphs.

## RESULTS

Samples were taken from total of 60 patients. Their distribution by gender is presented in Figure 1, and age distribution (by age categories) in Table 1 and Figure 2.

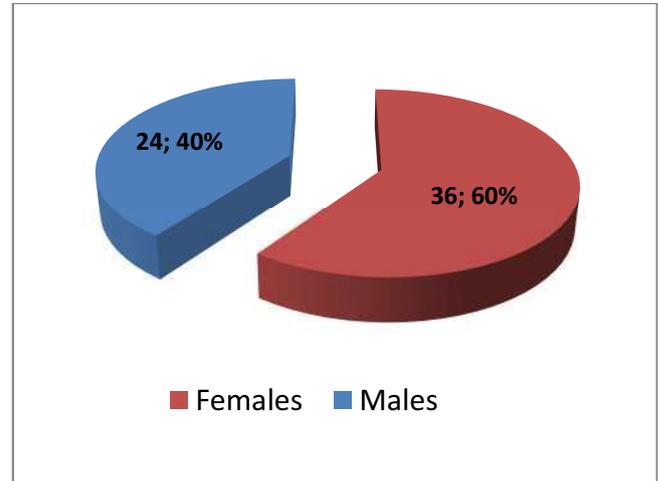


Figure 1 Distribution of participants by gender.

Out of total number of participants (60), majority were females (60 %, i.e. 36) and 40% (24) were males.

Table 1 Distribution of participants by age.

Age category (years)	No	(%)	Cumulative frequency ( $\omega$ )
18-25	22	(36,7)	36,7
26-35	29	(48,3)	85,0
36-42	9	(15,0)	100,0
<i>Total</i>	60	(100,0)	

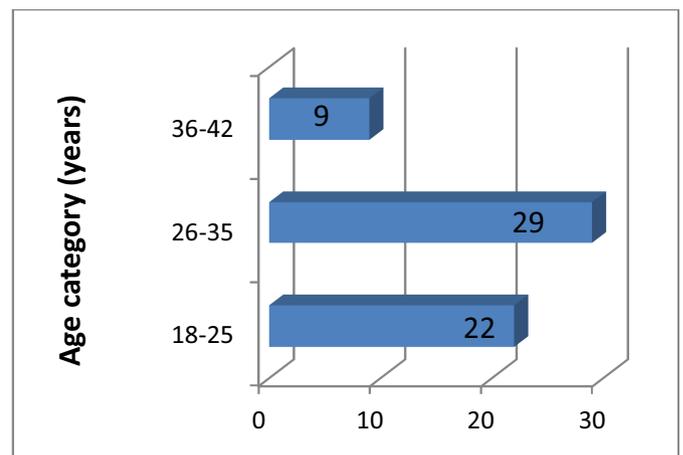


Figure 2 Distribution of participants by age.

The values of serum 25(OH)D level registered participants are shown in the box plot diagram (Figure 3).

Table 2 Descriptive statistics of D vitamin (ng/mL).

	1 Checkup	2 Checkup	3 Checkup	4 Checkup
Minimum	1.8	5,8	18	25
25th Percentile	6.115	18	26	33
Median	8.875	21	29	37
75th Percentile	12.85	26	31	40.25
Maximum	20.3	31	41	55
Mean	9.518	21.29	28.57667	37.415
Range	18.5	25.2	23	30
Standard deviation	4.810	5.176	4.597	5.807

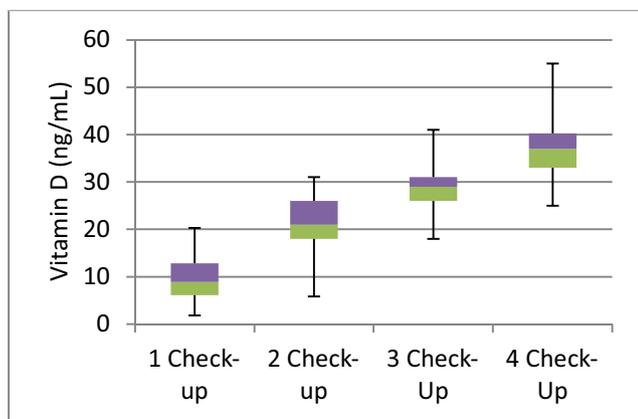


Figure 3 Boxplot of serum vitamin D levels.

Table 3 Descriptive statistics of TSH values (uIU/mL).

	1 Check-up	2 Check-up	3 Check-up	4 Check-up
Minimum	7.9	2,6	3,4	2,9
25th Percentile	22	6,075	4,2	3,6
Median	28.5	9,6	4,85	3,85
75th Percentile	35.5	14,25	5,275	4
Maximum	100	42	12,1	4,2
Mean	32.2683 3	11,71	5,35833 3	3,748333
Range	92,1	39,4	8,7	1,3
Standard deviation	17,464	7,741	1,887	0,354

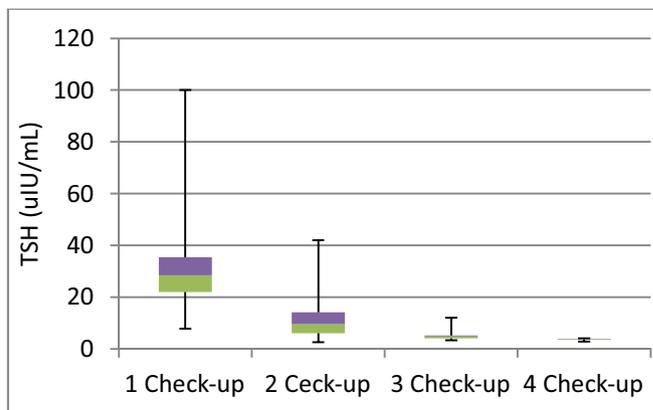


Figure 4 Boxplot TSH levels.

Table 4 Differences in Vitamin D values (ng/mL) between intervals (I-4 check-up).

	N	Mean Rank	Chi Square	P value
Checkup I	60	33.55	198.821	<0.001
Checkup II	60	96.68		
Checkup III	60	146.86		
Checkup IV	60	204.92		

Kruskal Wallis test showed a statistically significant difference in values of Vitamin D (ng/mL) between check-ups, with p <0.001.

Table 5 Differences in TSH values (uIU/mL) between intervals (I-4 Check-up).

	N	Mean Rank	Chi Square	P value
Checkup I	60	204.34	191.265	<0.001
Checkup II	60	146.13		
Checkup III	60	94.71		
Checkup IV	60	36.82		

Kruskal Wallis test showed a statistically significant difference in values of TSH (uIU/mL) between check-ups, with p <0.001.

Table 6 Correlation between Vitamin D (ng/mL) and TSH values (uIU/mL).

			Vitamin D
Spearman's correlation	TSH	Spearman's rho	-0,836
		P value	<0,001

Spearman's correlation between TSH and Vitamin D, showed a statistically significant negative correlation between the two, with p <0.001.

## DISCUSSION

Down's syndrome (DS), or trisomy of chromosome 21, is the most common genetic disorder associated with autoimmune diseases (7,8). DS is associated with increased risk of medical problems including gastrointestinal, cardiac, and pulmonary anomalies as well as developmental delay and endocrine abnormalities (4). Among the endocrine abnormalities, thyroid dysfunction is the commonest. It is estimated to occur in 4-8% of children with Down syndrome. The spectrum of thyroid dysfunction in patients with DS include congenital hypothyroidism, subclinical hypothyroidism, acquired hypothyroidism (autoimmune – non autoimmune), and hyperthyroidism (9,10).

Hypothyroidism (an underactive thyroid) is the type that most frequently occurs, and it is estimated that 13 percent to 55 percent of people with Down syndrome will develop the condition over the course of their lifetime (11,12) (on average, thyroid disease affects approximately 12 percent of the general population) (13).

It was suggested that treatment of TSH be reserved to patients who progress to overt hypothyroidism, and those with TSH > 10 µU/mL in the presence of goitre or positive thyroid auto antibodies.

Vitamin D plays a very important role in the immune response (14). It was established that it is connected with metabolic and immune processes in the body (15). It is defined as an immune modulator. It has roles in the regulation of cell growth, proliferation and apoptosis. It works by strengthening the immune system when it weakens, and reduces the immune response when it is too strong (16), which is the case with autoimmune diseases (1,2, 17).

At the turn of the century, a pathological association between Down syndrome and thyroid disorders was described by Bournville in 1903 (18). Clinical and histo-pathological confirmation was soon followed by Hill B and Gordon MB (19,20). However, the first case of a person with Down syndrome and clinical hyperthyroidism was reported by Gilchrist L in 1946 (21) and of clinical hypothyroidism by Maranon G, et al. in 1951 (22).

Thyroid disease in the Down syndrome population continues to be the focus of ongoing interest and research (23). This review collates previous research in the area of thyroid disorder and Down syndrome and explores aspects in need of further enquiry.

Many publications have suggested an association between Down syndrome and thyroid disorders by showing altered levels of abnormal thyroxine (T4), triiodothyronine (T3) and/or thyroid stimulating hormone (TSH) levels. Such changes may be present along with other hormonal and biochemical disturbances. The thyroid function tests documented a higher average TSH level in Down's syndrome than in other mentally retarded patients (24).

Research of Pierce MJ, et al. was that Thyroid disease in DS is more common and occurs earlier than in the general population, and is often transient. Thyroid disease is unrelated to gender, obesity, or other comorbidities (25).

Conclusion of researchs McGowan S, et al. and Murphy J, et al. was that Capillary TSH screening in Down's syndrome is eminently feasible and should be performed annually from 1 year of age. Nearly all subjects with initial venous TSH  $\geq$  11.0 mU/l will require thyroxine treatment but most with TSH 6-10 mU/l only require surveillance initially (26,27).

In patients who already have an autoimmune disease, vitamin D supplementation reduces the progression of the disease and stabilizes the condition (28). Prevention and therapy with vitamin D, calcium and other supplements are extremely important (29,30).

## CONCLUSION

The results of the study show that hypovitaminosis D and hypothyroidism are very frequent in DS individuals and that it is critical to assess the importance of vitamin D prophylaxis in these subjects and prescribe therapy with levothyroxine tablets. DS patients who have a history of autoimmune diseases may need more 25(OH)D supplementation.

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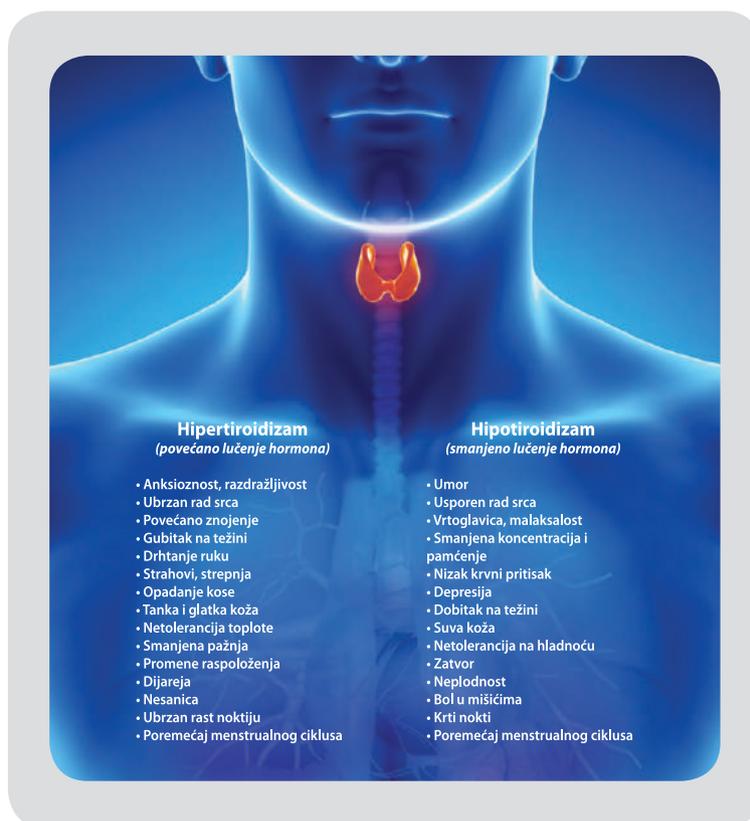
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# MSCT coronarography as part of the diagnostic modality of complex coronary artery disease: single center experience

## MSCT koronarografija kao dio dijagnostičkog modaliteta kompleksne koronarne arterijske bolesti: iskustvo jednog centra

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### ABSTRACT

Introduction: MSCT coronarography is non-invasive cardiac imaging modality as alternative to invasive cardiac angiography. The gold standard for diagnosing CAD is coronarography. Aim: to present the use of Multi-Slice Computed Tomography (MSCT) for the purpose of diagnostic evaluation of patient with complex coronary artery pathology. Materials and methods: in a period of two-year three groups of patients with calcium score (CAC) at the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo were reviewed. We analysed CAD findings based on calcium score risk. Results: we examined three groups of patients with CAC score; group with a low to mild risk of CAD (calcium score 0-99) n-320 (39.6%), moderate risk of CAD (calcium score 100-400) n-314 (38.8%) and high risk of CAD (Calcium score >400) n-174 (21.6%). Patients with a low CAD risk had a mean CAC score of  $54.1 \pm 13.2$ . Even though patients with low to mild CAC score have a low risk of future cardiovascular events, in two cases, on coronary angiography we found: subocclusion of the ramus intermedius with soft tissue plaque (calcium score was 96), and in the second case presence of a bridge on the left anterior descending (LAD) artery (calcium score was 0). In group with moderate CAD risk, CAC score was  $245.5 \pm 16.3$ . In this group the vast majority did conduct coronary angiography. Here we found significant CAD stenosis in n-195 (62.0%). In group of high risk of CAD (>400), we found calcium score  $643.9 \pm 53.2$ . In this group patients with a calcium score > 1000 were immediately referred for coronary angiography. Conclusion: MSCT coronary angiography is an important factor in the diagnostic evaluation of patient referred to cardiac surgery as well for a follow up after coronary angiography or surgery.

**Keywords:** MSCT, calcium score, cardiac surgery

### SAŽETAK

Uvod: MSCT koronarografija je neinvazivni modalitet snimanja srca kao alternativa invazivnoj angiografiji srca. Zlatni standard za dijagnosticiranje CAD je koronarna angiografija. Cilj: predstaviti upotrebu višeslojne kompjuterizovane tomografije (MSCT) u svrhu dijagnostičke evaluacije pacijenata sa složenom patologijom koronarnih arterija. Materijal i metode: u periodu od dvije godine pregledane su tri grupe pacijenata sa calcium score (CAC) na Klinici za kardiovaskularnu hirurgiju Kliničkog centra Univerziteta u Sarajevu. Analizirali smo CAD nalaze zasnovane na riziku na osnovu kalcijum-skor izračuna. Rezultati: ispitivali smo tri grupe pacijenata sa CAC skorom; grupa sa niskim do blagim rizikom od CAD (kalcij skor 0-99) n-320 (39,6%), umjerenim rizikom od CAD (kalcij skor 100-400) n-314 (38,8%) i visokim rizikom od CAD (kalcij skor >400) n-174 (21,6%). Pacijenti sa niskim rizikom od CAD imali su srednji CAC skor od  $54,1 \pm 13,2$ . Iako pacijenti sa niskim do blagim CAC skorom imaju nizak rizik od budućih kardiovaskularnih događaja, u dva slučaja koronarografijom smo utvrdili: subokluziju ramus intermediusa sa mekim tkivnim plakom (kalcijumski skor 96), u drugom slučaju prisustvo mosta na levoj prednjoj silaznoj (LAD) arteriji (kalcijumska ocjena je bila 0). U grupi sa umjerenim rizikom od CAD, CAC skor je bio  $245,5 \pm 16,3$ . U ovoj grupi velika većina je radila koronarografiju. Ovdje smo pronašli značajnu CAD stenozu u n-195 (62,0%). U grupi visokog rizika od koronarne bolesti (>400) nalazimo calcium score  $643,9 \pm 53,2$ . U ovoj grupi, pacijenti sa skorom kalcijuma > 1000 bili su odmah upućeni na koronarografiju bez obzira na to. Zaključak: MSCT koronarna angiografija je važan faktor u dijagnostičkoj evaluaciji pacijenata upućenih na kardiohirurgiju, kao i za praćenje nakon koronarne angiografije ili operacije.

**Ključne riječi:** MSCT, kalcijum skor, kardiohirurgija

## INTRODUCTION

A Heart Team (HT) was organised at the Clinical Center University of Sarajevo (CCUS), consisting of cardiovascular surgeon, interventional cardiologist and cardiologist in addition to them other specialities or even family doctor for palliative care can be included.

Multi-Slice Computed Tomography (MSCT) is a non-invasive diagnostic radiological-cardiology method, which records changes in coronary blood vessels with the help of multi-slice detectors and computer software, and after the application of contrast medium - intravenously (1). MSCT represents a diagnostic method that is of great importance for HT. The final result is a three-dimensional representation of the coronary artery system. MSCT has the ability to determine the calcium score, observe the qualitative characteristics of the atherosclerotic plaque, the ability to detect "suspicious" findings - e.g. thrombus in the heart cavities, display anomalous starting points of the coronary system, and the patency of aortocoronary bypass grafts, as well as vein drainage route, other congenital heart diseases. (Figure 1) (2,3). Patients with a previously placed stent are not the best candidates for MSCT due to the possible occurrence of a blurring phenomenon, when calcifications that are more expressive mask the lumen of the coronary blood vessel located below the stent.

Generally, MSCT coronarography is commonly indicated to rule out obstructive CAD in symptomatic patients, ergo test positive or borderline with low or intermediate risk for CAD, in high risk non-cardiac surgery where invasive coronarography can be dangerous, acquired and congenital heart disease with low risk for CAD (4). AHA/ACC did not recommend use of MSCT for screening of CAD in every asymptomatic patient.

MSCT coronarography have high negative predictive value and is most useful for evaluation patients at low to intermedium risk for CAD and who are at borderline or clearly symptomatic.

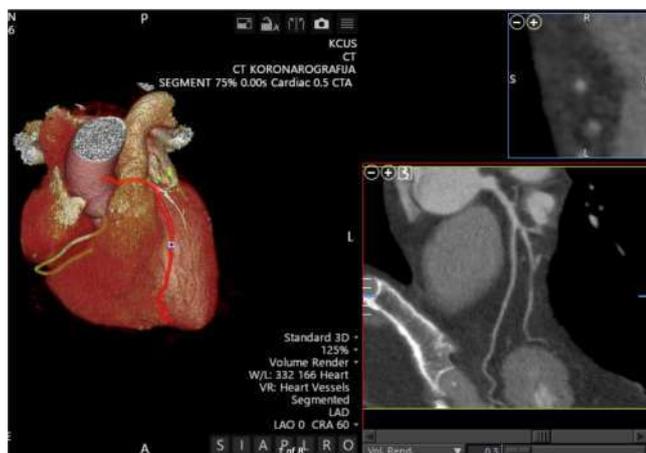


Figure 1 Multi-Slice Computed Tomography (MSCT).

## AIM

The aim of the study was to present the use of Multi-Slice Computed Tomography (MSCT) for the purpose of diagnostic evaluation of patients with complex coronary artery pathology.

## MATERIALS AND METHODS

A total of 1105 patients were treated at the Clinic of Cardiovascular Surgery of the CCUS in the period from January 2020 to December 2021. Based on Calcium score (CAC) patients were divided into three groups: low, medium and high score group. For each of the groups we calculate percentage of confirmed severe coronary artery disease by coronarography.

The Coronary calcium score is used to quantify coronary calcium level (5). It is a test that measures the location and extent of calcium in the coronary arteries. Based on that finding we can suggest presence of subclinical or advanced coronary artery disease. Also it can be used as substitute for standard risk factors in predicting CAD risk.

Any calcium score over 400 is correlated with an increased risk of cardiac death (over 20%), while a score over 1000 represents extensive calcium accumulation (6).

Vulnerable soft tissue plaques do not contain calcium in their composition, and for this reason this grading is not specific, but it is used in assessing the degree of development of atherosclerosis, as well as assessing the prognosis of the disease and grading the risk of cardiac death.

Prior MSCT procedure beta blocker and sublingual nitrates have to be administered in order to lower heart rate, avoid arrhythmia and dilate the coronary arteries. Also, synchronous ECG monitoring is applied. Although the most desirable heart rate is between 50-55/min, the rate of up to 65/min is tolerated. As MSCT use contrast medium that could be nephrotoxic, urea and creatinine laboratory findings are obligatory.

## RESULTS

The Clinic of Cardiovascular Surgery performed 1105 cardiac procedures in the period from January 2020 to December 2021. Out of the total number of patients to whom MSCT was indicated, 297 (26.9%) failed an attempt of the MSCT performing (Figure 2). In 3 (0.3%) patients who were with previously implanted electrostimulator, the MSCT was performed only after therapy optimization.

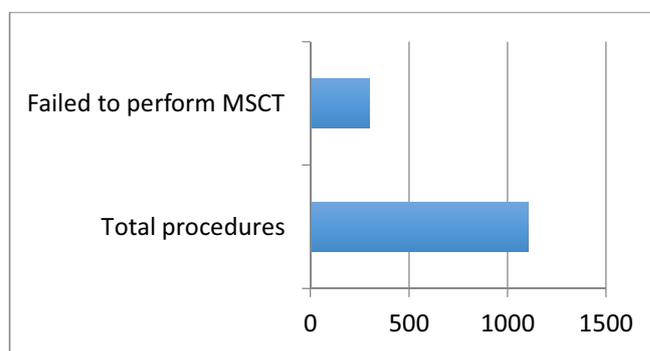


Figure 2 Number of patients that failed to perform MSCT.

In 2 (0.2%) cases, the examination was stopped before the last contrast series due to a rhythm disturbance, and in one patient (0.1%) the examination was brought to an end, but it was not possible to read it due to artefacts. In 3 (0.3%) cases, we had patients with a rhythm disorder of the type of atrial fibrillation with a ventricular response above the cut-off value of 65/min. In two (0.2%) cases, we had patients with atrial fibrillation with proper ventricular

response, below 65/min, who regularly underwent MSCT. Given that the Clinic of Radiology offers the possibility of repeating the MSCT procedure for the same patient up to 4 times, that protocol was used, and two patients managed to undergo MSCT in the third attempt. Of the total number of patients, 212 (19.2%) were patients who, in addition to valvular disease, were also diagnosed with coronary disease (Figure).

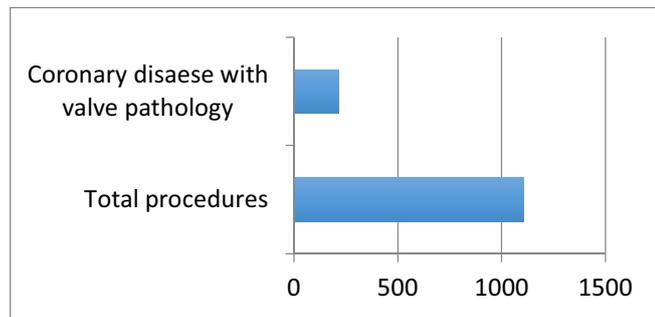


Figure 3 Patients with coronary disease along with valve pathology.

We examined three groups of patients with Calcium (CAC) score and compared CAD risk with CAC score. The group with a low to mild risk of CAD included n-320 (39.6%) patients, the group with moderate risk of CAD n-314 (38.8%) and the group with higher risk of CAD n-174 (21.6%) patients.

Patients with a low CAD risk had a mean CAC score of  $54.1 \pm 13.2$  ranging from 0 to 99. The majority of patients 318 (99.4%) in this group were discharged from hospitalisation with an advice on risk factors control (hypertension, diabetes mellitus, obesity, diet and other factors) Even though patients with low to mild CAC score have a low risk of future cardiovascular events, in two cases, patients with a low calcium score were also sent for coronary angiography on the recommendation of the interventional cardiologist. In the first case, due to the described soft tissue plaque that leads to subocclusion of the ramus intermedius (Ca score=96), and in the second Ca score=0 due to the presence of a bridge on the left anterior descending (LAD) artery.

The group of moderate CAD risk had CAC score of  $245.5 \pm 16.3$  ranging from 100 to 400. All patients were recommended to do a coronary angiography due to moderate risk of CAD. The vast majority did conduct coronary angiography with significant stenosis of the coronary arteries n-195 (62.0%)

In the group of higher risk for CAD (>400), mean CAC score was  $643.9 \pm 53.2$  ranging from 400 to 1400. Patients with a CAC score >1000 were referred for mandatory coronary angiography. Part of this group related to patients who were already in preoperative preparation at the Clinic of Cardiovascular Surgery n-54, and 2 patients had already undergone surgery (RE-DO operation was performed after coronary angiography).

All CAD risk, sex, age, risk factors and CAC score among patients presented to the HT between 2020 and 2021 are presented in Table 1.

Table 1 CAD risk, sex, age, risk factors and CAC score among observed patients between 2020 and 2021.

		CAC score (0-99) (N=320)	CAC score (100-400) (N=314)	CAC score (>400) (N=174)
CAD Risk		Low to mild	Moderate	Higher
Sex	Male	239 (74.7%)	213 (67.8%)	95 (54.6%)
	Female	81 (25.3%)	101 (32.2%)	79 (45.4%)
Age	mean $\pm$ SD	53.5 $\pm$ 3.4	58.2 $\pm$ 5.3	65 $\pm$ 4.3
Risk factors	Hypertension	240 (75.0%)	234 (74.5%)	105 (60.3%)
	Diabetes mellitus	67 (20.9%)	73 (23.3%)	46 (26.4%)
	Hyperlipidemia	74 (23.1%)	83 (26.4%)	58 (33.3%)
	Overweight	143 (44.6%)	152 (48.4%)	105 (60.3%)
	Smoking	174 (54.3%)	123 (39.1%)	95 (54.6%)
CAC score	mean $\pm$ SD	54.1 $\pm$ 13.2	245.5 $\pm$ 16.3	643.9 $\pm$ 53.2

Table 2 Comparison of Calcium score and Coronarography.

MSCT Calcium score (mean $\pm$ SD)	Confirmed on coronarography	Futher plan
Low group (54.1 $\pm$ 13.2)	1 (0,1%)	HT decision to stay on MSCT or to perform Coronarography
Medium group (245.5 $\pm$ 16.3)	195 (17,5%)	Perform Coronarography
High group (643.9 $\pm$ 53.2)	172 (15,0%)	Perform Coronarography

Our results, showed that higher CAC score on MSCT angiography, followed by a coronary angiography led to a more rational use of coronary angiography and more precise target of severe CAD patients.

## DISCUSSION

In recent decades, due to the socio-epidemiological situation, as well as congenital and uncontrolled acquired risk factors, our society has been struggling with the tendency of a constant increase in the number of people suffering from cardiovascular diseases; coronary and valvular. Patients with pronounced cardiac symptoms are referred for diagnostic procedures, on the basis of which an indication for active cardio surgical treatment can be established. Nevertheless, the gold standard in diagnostic terms, when it comes to patients with coronary artery disease, is coronary angiography (7). Coronary angiography is an interventional cardiology procedure, with the help of which the coronary blood vessels are visualized with X-rays, after the intravenous application of an iodine contrast agent with the help of a catheter, using the Seldinger method. However,

the question arises, is coronary angiography, as a preoperative diagnostic procedure, necessary for patients with valvular heart disease. This is important especially in age groups (<40 and >40years) (8).

Waiting lists for coronary angiography are long. Regardless of all the human resources, daily work and commitment of doctors, patients can wait up to a year for this examination. In that year, according to the criteria, reversible changes in the myocardium can become irreversible, satisfactory heart power - reduced, insignificant changes in the coronary blood vessels can become subocclusions, and mild or moderate changes in the valves become severe, even in old age. A patient in good psychophysical condition, with potentially good "timing" for surgery and an expected good outcome, becomes an inoperable, psychologically altered, dissatisfied patient, with premature heart valve changes.

Both mentioned diagnostic procedures have their advantages and disadvantages. MSCT Coronarography has high negative predictive value (between 95-100%, if using conventional coronarography as a reference standard) (9). So it is the most useful tool in evaluating low to intermediate risk for CAD by excluding CAD after obtaining negative results on MSCT (10). This exclusion last for 5-7 years, which means that patients could avoid future unnecessary ischemic testing with a risk of MACE in <1%. It can be consider as non-invasive or semi-invasive procedure. Depending of equipment, scanning can be performed from 40 through 10 seconds or even shorter.

Coronary angiography, as an invasive diagnostic discipline, requires pre-procedural hospitalization of the patient and a generally longer hospital stay (11). Considering that the access of the catheter is invasive, usually through the femoral artery or the radial artery, the possibility of post-procedural complications is higher; loss of pulse distal to the puncture site, i.e. compression, bleeding, formation of hematoma, pseudoaneurysm, arterial-venous fistula. If the access point is through the femoral artery, it is necessary to rest in a horizontal position with the limb extended for 6 or 12 hours after the procedure, and verticalization is performed the day after the procedure. During the procedure, malignant rhythm disorders, accidental traumatic perforation of the coronary blood vessel are possible. All this makes the given method more expensive and increases the cost of hospital treatment.

HT on the CCUS was formed with the desire to try to overcome all the above challenges. Valvular heart disease can be considered as separate group of disease, with assumption that there are no significant changes in the coronary blood vessels, if there is no other risk for CAD. After clinical and ultrasonographically confirmation of severe valvular disease which require surgical correction patient is presented for HT decision. The patient presented to HT and is referred to the MSCT coronary angiography procedure or conventional coronarography. Based on our data and literature age can be consider the most important screening divider for low risk CAD as there is drastically decrease in incidence of CAD as age decrease. Table 2 suggests HT to perform MSCT only in age <40years. Also, there are even softer concepts suggesting that MSCT coronarography be performed on all valvular patients. The originator of this diagnostic protocol is professor Zamorano J, (13-15), whose initial ideas and realizations we, as part of the Clinic of Cardiovascular Surgery and HT, managed to realize with the aim of providing the best possible medical service in which the individual patient - an individual, different from all others, received an individual diagnostic and therapeutic approach, with the reduction of the waiting list, reduced costs of medical services, and ideal "timing" for the operation. As it was said at the beginning, HT is at the very beginning of its activity, with the hope that this approach to the patient and

diagnostic protocol will be adopted as a standard not only in the field of cardiac surgery but also in other branches of medicine.

## CONCLUSION

MSCT coronary angiography is an important factor in the perioperative treatment of cardiac surgery patients. Our study, showed that higher CAC score on MSCT angiography, followed by a coronary angiography led to a more rational use of coronary angiography and more precise target of severe CAD patients. A multidisciplinary approach should be the path to the development of modern cardiac surgery.

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**Declaration of patient consent:** the authors certify that they have obtained all appropriate patient consent forms. In the form, patients have given their consent for their images and other clinical information to be reported in the journal.

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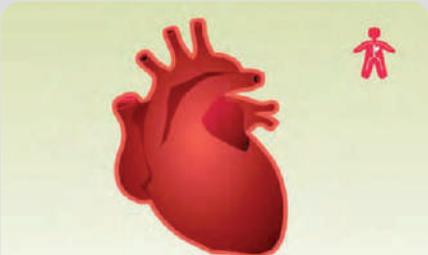
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Povišeni krvni pritisak, hipertenzija, jedan je od riziko faktora koji značajno pridonosi nastanku bolesti srca i krvnih sudova, vodećih uzroka smrtnosti i glavnog javnozdravstvenog problema svuda u svijetu.

# Uroflowmetry and post-void residual urine as tests to diagnose asymptomatic urethral obstruction in boys following urethral surgery or trauma

## Uroflowmetrija i rezidualni postmikcioni urin kao testovi za dijagnosticiranje asimptomatske opstrukcije uretre kod dječaka nakon operacije uretre ili traume

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### ABSTRACT

Introduction: Uroflowmetry (UF) and post-void residual urine (PVR) are the first steps in the evaluation of lower urinary tract symptoms (LUTS) and voiding dysfunction (VD) for both adults and children. Aim: to analyse and evaluate the accuracy of UF and PVR in the evaluation of children with LUTD caused by acquired infravesical obstruction of the urinary tract. Materials and methods: 68 boys with a history of previous urethral surgery or trauma were evaluated by studying their voiding history, a physical examination, UF, and suprapubic ultrasonography. The children were divided into two groups according to the existence or absence of LUTS: the first group included 33 boys with LUTS (obstructive group) and the second group included 35 asymptomatic boys with the absence of LUTS (non-obstructive group). All uroflowmetry data, including maximum flow rate (Q<sub>max</sub>), voided volume (VV), time to Q<sub>max</sub>, voiding time (V<sub>t</sub>), average flow rate (Q<sub>ave</sub>), uroflow patterns as well as post-void residual urine (PVR) are recorded and analyzed. Results: the mean age was 3.84 ± 3.08 years. Except for VV and flow time, all UF components were significantly different between obstructive and non-obstructive groups. Q<sub>max</sub> was smaller in the obstructive group (4.9 ± 2.32 vs. 10.34 ± 4.82, p<0.001). Time to Q<sub>max</sub> was greater in the obstructive group (66.27 ± 197.7 vs. 12.97 ± 25.7, p<0.001). Also, V<sub>t</sub> was greater in the obstructive group (100.36 ± 234.07 vs. 28.71 ± 26.41, p<0.001). Q<sub>ave</sub> was smaller in the obstructive group (3.27 ± 1.71 vs. 5.58 ± 3.09, p<0.001). PVR was greater in the obstructive group (37.78 ± 48.75 vs. 13.17 ± 28.91, p<0.001). The boys in the obstructive group had a significantly increased risk of non-bell-shaped urination (plateau or interrupted patterns) compared with boys in the non-obstructive group. Conclusion: our findings suggest that UF and PVR used in daily pediatric urology practice are methods capable of identifying asymptomatic meatal or urethral obstruction in boys with a previous history of urethral surgery or trauma determining response to treatment of lower urinary tract disorders.

**Keywords:** uroflowmetry, post-void residual urine, urethral surgery, urethral trauma

### SAŽETAK

Uvod: uroflowmetrija (UF) i rezidualni urin nakon mokrenja (PVR) predstavljaju prve korake u evaluaciji simptoma donjeg urinarnog trakta (LUTS) i disfunkcije mokrenja (VD) kod odraslih i djece. Ovo istraživanje je imalo za cilj analizirati tačnost uroflowmetrije i rezidualnog urina u procjeni i dijagnosticiranju opstrukcije uretre kod dječaka nakon operacije uretre ili traume. Cilj: analizirati i ocijeniti tačnost UF i PVR u evaluaciji djece s LUTD-om uzrokovanom stečenom infravezikalnom opstrukcijom urinarnog trakta. Materijali i metode: 68 dječaka s historijom prethodnih operacija uretre ili traume evaluirano je proučavanjem njihove historije mokrenja, fizikalnim pregledom, UF-om i suprapubičnim ultrazvukom. Djeca su podijeljena u dvije grupe prema prisustvu ili odsustvu LUTS-a: u prvoj grupi bilo je 33 dječaka s LUTS-om (opstruktivna skupina), a u drugoj grupi 35 asimptomatskih dječaka s odsustvom LUTS-a (neopstruktivna skupina). Svi podaci uroflowmetrije, uključujući maksimalni protok (Q<sub>max</sub>), izmokrenu količinu mokraće (VV), vrijeme do Q<sub>max</sub>, vrijeme mokrenja (V<sub>t</sub>), prosječnu brzinu protoka (Q<sub>ave</sub>), obrasce uroflowa, kao i rezidualni urin nakon mokrenja (PVR) su bili zabilježeni i analizirani. Rezultati: prosječna dob bila je 3,84 ± 3,08 godina. Osim VV i vremena protoka, sve komponente UF su se značajno razlikovale između opstruktivne i neopstruktivne grupe. Q<sub>max</sub> je bio manji u opstruktivnoj grupi (4,9 ± 2,32 prema 10,34 ± 4,82, p<0,001). Vrijeme do Q<sub>max</sub> bilo je veće u opstruktivnoj grupi (66,27 ± 197,7 naspram 12,97 ± 25,7, p<0,001). Također, V<sub>t</sub> je bio veći u opstruktivnoj grupi (100,36 ± 234,07 prema 28,71 ± 26,41, p<0,001). Q<sub>ave</sub> je bio manji u opstruktivnoj grupi (3,27 ± 1,71 naspram 5,58 ± 3,09, p<0,001). PVR je bio veći u opstruktivnoj grupi (37,78 ± 48,75 prema 13,17 ± 28,91, p<0,001). Dječaci u opstruktivnoj skupini imali su značajno povećan rizik od nezvonolikog oblika krivulje mokrenja (plato ili isprekidani uzorci) u

poređenju s dječacima u neopstruktivnoj grupi. Zaključak: naši rezultati sugerišu da su UF i PVR koji se koriste u svakodnevnoj pedijatrijskoj urološkoj praksi metode koje mogu identificirati asimptomatsku meatalnu ili uretralnu opstrukciju kod dječaka s

prethodnom historijom uretralnih operacija ili trauma, determinirajući odgovor na liječenje poremećaja donjeg urinarnog trakta.

**Ključne riječi:** uroflowmetrija, rezidualni urin nakon mokrenja, uretralna operacija, uretralna trauma,

## INTRODUCTION

Uroflowmetry (UF) and post-void residual urine (PVR) are the most frequently used initial screening urodynamic tests when lower urinary tract dysfunction (LUTD), also known as dysfunctional voiding, is suspected (1). UF and PVR are screening tests that allow the proper selection of patients for more complex urodynamic testing and provide the information necessary to determine the appropriate treatment strategy (2).

Although tabularized incised plate (TIP) urethroplasty or Snodgrass procedure has gained worldwide acceptance for distal hypospadias repair due to highly acceptable functional and cosmetic results, complications associated with this procedure can be significant and include meatal stenosis, urethral fistula, dehiscence, and diverticulum (3). Some studies also determined the link between increased PVR and urinary tract infections (UTIs) in hypospadias operated by TIP (4,5) and found that the mentioned link can be attributable to a degree of increased resistance and outflow obstruction in the created neo-urethra (6). Lower urinary tract trauma, although relatively uncommon in blunt trauma, also can cause substantial morbidity with marked effects on quality of life (7,8).

## AIM

The aim of the study was to analyse and evaluate the accuracy of UF and PVR in the evaluation of children with LUTD caused by acquired infravesical obstruction of the urinary tract.

## MATERIALS AND METHODS

A retrospective medical records review was undertaken of all consecutive patients with a history of previous urethral surgery or trauma who underwent uroflowmetry and determining post-void residual urine from January 2017 to Mart 2018. Formal approval for the review of the medical records was obtained from the Ethics Committee of the Clinical Center University of Sarajevo.

UF and PVR were performed at the Pediatric Surgery/Urology Outpatient Department of the Clinical Center University of Sarajevo. PVR is defined as the volume of urine left in the bladder at the end of micturition. PVR measurement was performed immediately after the completion of uroflowmetry by ultrasonography. Voiding dysfunction (VD), a diagnosis by symptoms and urodynamic investigations, is defined as abnormally slow and/or incomplete micturition and abnormally high post-void residuals. Lower urinary tract symptoms (LUTSs) were the term used to describe a range of symptoms related to problems of the lower urinary tract (bladder, prostate, and urethra), although no such correlation exists between symptoms and underlying pathophysiology. By the type of symptoms, LUTS is divided into irritating symptoms (IS) and obstructive symptoms (OS). IS was defined as frequency, urgency, and urge incontinence. OS was defined as hesitancy, weak stream, straining, intermittency, and incomplete emptying. According to the definition provided by the International Children's Continence Society (ICCS), the urinary flow patterns (voiding curves) were divided into five groups: bell-shaped, tower-shaped, plateau, staccato, and interrupted,

and were read by a single pediatric urologist who was not blinded to patients voiding symptoms. The flow rate was considered valid if the voided volume was more than two-thirds of the expected bladder capacity. We analyzed study pediatric patients concerning age, maximal flow rate ( $Q_{max}$ ), voided volume, postvoid residual volume, serum PSA level, prostate volume, I-PSS, and the urodynamic variables.

## Statistical analysis

Statistical analysis used: Statistical Package for Social Science for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Student t-test and Mann-Whitney test were used to confirm statistical differences between analyzed groups. Statistical significance was considered as  $p < 0.05$ .

## RESULTS

A total of 68 patients were included in the study, 33 (48.5%) in the obstructive group and 35 (51.5%) in the non-obstructive group. The mean age of the entire cohort was  $3.84 \pm 3.08$  years. The age distribution of patients with a history of previous urethral surgery or trauma is shown in Table 1.

Table 1 The age distribution of patients with previous urethral surgery or trauma.

Age range (years)	Number (No.)	Percentage of total (%)
0-1 yr	14	20.6
2-3 yr	29	42.6
4-6 yr	16	23.5
7-10 yr	4	5.9
11-15 yr	5	7.4
Total	68	100

UF and PVR were done for the following clinical entities: post-hypospadias repair in 57 (83.8%), post-urethral valve fulguration in 3 (4.4%), post-circumcision meatal stenosis in 5 (7.4%), post-traumatic urethral stricture in 2 (2.9%) and post epispadias reconstructive surgery in 1 (1.5%). The age distribution of patients with or without acquired infravesical obstruction of the urinary tract is shown in Table 2.

Table 2 The age distribution of patients with vs without obstruction.

Age range (years)	Obstructive group	Non-obstructive group
	Number (No.) and Percentage of total (%)	Number (No.) and Percentage of total (%)
0-1 yr	7 (21.2%)	7 (20.0%)
2-3 yr	12 (36.4%)	17 (47.6%)
4-6 yr	10 (30.3%)	6 (17.1%)
7-10 yr	3 (9.1%)	1 (2.9%)
11-15 yr	1 (3.0%)	4 (11.4%)
Total	33 (100%)	35 (100%)

A significant difference between obstructive and non-obstructive groups ( $p < 0.05$ ) was detected in maximum flow rate ( $Q_{max}$ ), time to  $Q_{max}$ , voiding time ( $V_t$ ), average flow rate ( $Q_{ave}$ ), and post-void residual urine PVR (Table 3).

Table 3 Baseline data of patients and test results after evaluation with uroflowmetry and PVR in obstructive vs non-obstructive groups.

Parameter	Infravesical obstruction		P value
	YES	NO	
Age (yr)	3.75 ± 2.70	3.94 ± 3.81	0.819
Voided volume (VV)	173.3 ± 130.7	130.8 ± 97.84	0.149
Maximum flow rate ( $Q_{max}$ )	4.9 ± 2.32	10.34 ± 4.82	0.0001
Time to $Q_{max}$	66.27 ± 197.7	12.97 ± 25.7	0.0001
Voiding time ( $V_t$ )	100.36 ± 234.07	28.71 ± 26.41	0.0001
Flow time	93.24 ± 145.6	77.2 ± 148.53	0.394
Average flow rate ( $Q_{ave}$ )	3.27 ± 1.71	5.58 ± 3.09	0.0001
Post-void residual urine (PVR)	37.78 ± 48.75	13.17 ± 28.91	0.001

In the uroflowmetric analysis, 20/35 (57.1%), 7/35 (20%), 6/35 (17.1%), and 2/35 (5.7%) boys in the non-obstructive group showed a bell-shaped, interrupted, plateau and tower-shaped patterns, respectively (Figure 1). In contrast, 1/33 (3.0%), 18/33 (54.5%), 11/33 (33.3%), and 3/33 (9.1%) boys in the obstructive group showed a bell-shaped, interrupted, plateau and staccato patterns, respectively (Figure 2). Therefore, the boys in the obstructive group had a significantly increased risk of non-bell-shaped urination (plateau or interrupted patterns) compared with boys in the non-obstructive group (OR 12.3, 95%CI 3.54-42.5).

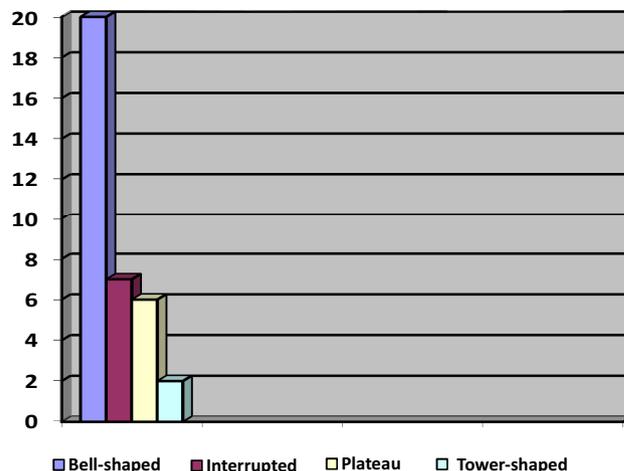


Figure 1 Voiding flow patterns (voiding curves) in non-obstructive group.

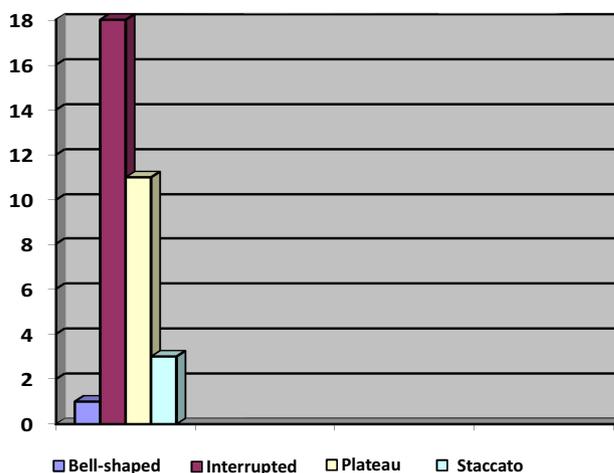


Figure 2 Voiding flow patterns (voiding curves) in obstructive group.

## DISCUSSION

This study highlights the role of UF and PVR as non-invasive tests in the detection of acquired infravesical obstruction of the urinary tract and voiding dysfunction (VD) in pediatric patients with previous urethral surgery or trauma.

VD represents a broad term used to describe a voiding pattern that is abnormal for a child's age. Diagnosis of VD in children is often a challenging task for pediatric urologists. Although the full urodynamic examination is a reliable test, it is also very invasive and traumatic for children. Also, some studies have shown a limited value of full urodynamic testing in diagnosing VD in children (9). In conjunction with a history of illness and physical examination, UF is a useful tool for identifying children with voiding dysfunction as well as for determining responses to the treatment of lower urinary tract disorders of this age population (2). Some studies have shown the utility of UF in the functional evaluation of children with reconstructed urethra due to hypospadias, especially in the detection of symptomatic and asymptomatic urethral strictures (10-12). These studies have shown that children with a flow rate of 2 SD below the

mean or those with flat voiding curves have a high likelihood of postoperative urethral pathology in the form of urethral obstruction (10-12). Our study confirmed these findings.

Based on ICCS recommendations, uroflowmetry curves are classified into five types, bell, tower, plateau, staccato and interrupted (fractionated) of which only bell-shaped curves are considered as normal (5,9). Recorded rates of a normal bell-shaped uroflow pattern in healthy children range from 63% to 97.2% (13-15). In our research, 57.1% of children who did not have symptoms of LUTS and who were included in the non-obstructive group had bell-shaped uroflow patterns. There are several possible explanations for our findings of a somewhat lower frequency of bell-shaped patterns in children without symptoms of LUTS. Some of the possible explanations include the simple fact that non-bell-shaped curves are noticeably more frequent in voiding with bladder overdistension than those without overdistension (16,17). Contrary to the above, we found that 3.0%, 54.5%, 33.3%, and 9.1% of boys in the obstructive group showed bell-shaped, interrupted, plateau, and staccato patterns, respectively. These findings are in agreement with the findings of other studies (18,19).

The findings of previous studies on normal average PVR indicate that PVP is less than 10 ml, with no relationship with age, sex, or voided volume in children with a normal voiding pattern (5,20,21). Jansson et al reported that the mean PVP in the age group of children up to 6 years with normal voiding pattern was from 0 to 5.5 ml (22). On the other hand, the absence of PVR does not exclude infravesical obstruction or bladder-sphincter dysfunction (23). Although mean PVR values for boys include in the present study were higher than the normal values for children with normal voiding pattern and no LU DT (13.17 ± 28.91), it should be noted that the boys in the non-obstructive group had previous operative procedures on their urethra. The assessment of the success of surgical treatment in the non-obstructive group in relation to the obstructive group is reflected in statistically significantly smaller PVR in the non-obstructive group ( $p=0.001$ ) which is in agreement with the results of other studies (24).

## CONCLUSION

Uroflowmetry and post-void residual urine are important screening tools in the evaluation of LU DT because they can detect the general performance of bladder contractility and bladder outlet resistance and thus select patients who require additional medical and/or surgical treatment.

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# Early results of carotid endarterectomy in diabetic patients with symptomatic stenosis

## Rani rezultati karotidne endarterektomije kod dijabetičara sa simptomatskom stenozom

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### ABSTRACT

Introduction: Carotid endarterectomy (CEA) is an effective and safe treatment for carotid artery stenosis. Aim: to compare early outcomes after carotid endarterectomy between patients with diabetes mellitus (DM) and patients without diabetes mellitus with symptomatic carotid artery stenosis. Materials and methods: we retrospectively analyzed 161 CEAs, which were performed in patients with symptomatic carotid artery stenosis, between January 2018 and May 2022. CEAs were divided into a DM group (n=58; 36%) and a non-DM group (n=103; 64%). Study outcomes included the incidence of major adverse events (MAEs), defined mortality, stroke and myocardial infarction (MI) during the early perioperative period (0-30 days). Results: there was no statistically significant difference between the analyzed groups regarding total complications (3.4% vs 2.9%;  $P>0.05$ ). Statistically significant differences were recorded in the presence of bilateral stenosis (31% vs 16.5%;  $P=0.046$ ), peripheral arterial occlusive disease (32.8% vs 16.5%;  $P=0.029$ ) in patients with DM. Despite these differences, patients with DM had similar perioperative outcomes compared with non-diabetic patients, including perioperative MI (1.7% vs. 0.97%;  $P=0.974$ ), perioperative death (1.7% vs. 0.97%;  $P=0.974$ ), and perioperative neurologic events such as stroke (0% vs. 0.97%;  $P=0.770$ ). No differences in demographic factors were noted between diabetic and non-diabetic patients. Conclusions: despite the increased prevalence of bilateral stenosis and peripheral arterial occlusive disease in patients with diabetes who underwent CEAs, the rates of perioperative morbidity and mortality were without statistically significant differences.

**Keywords:** symptomatic carotid artery stenosis, carotid endarterectomy, diabetes mellitus

### SAŽETAK

Uvod: karotidna endarterektomija (CEA) je učinkovit i siguran tretman stenozе karotidnih arterija. Cilj: uporediti rane ishode nakon karotidne endarterektomije (CEA) između bolesnika s dijabetesom i nedijabetičara sa simptomatskom stenozom karotidnih arterija. Metode: retrospektivno smo analizirali 161 CEA, koji su provedeni pacijenatima sa simptomatskom stenozom karotidnih arterija, između januara 2018. i maja 2022. CEA su podijeljeni u skupinu sa dijabetesom (DM) (n=58; 36%) i ne-DM skupinu (n=103; 64%). Rezultati studije uključivali su incidenciju velikih nuspojava (MAE), definirani kao smrtonost, nefatalni moždani udar i infarkt miokarda tokom ranog perioperativnog perioda (0-30 dana), nakon CEA, kod pacijenata sa simptomatskom stenozom. Rezultati: nije bilo statistički značajne razlike između analiziranih skupina u pogledu ukupnih komplikacija (3,4% vs. 2,9%;  $P>0,05$ ). Evidentirana je statistički značajna razlike u prisustvu bilateralne stenozе (31% vs 16,5%;  $P=0,046$ ) i periferne arterijske okluzivne bolesti (32,8% vs. 16,5%;  $P=0,029$ ) kod pacijenata sa DM. Unatoč tim razlikama, bolesnici sa dijabetesom imali su slične perioperativne ishode u komparaciji sa pacijentima bez dijabetesa, uključujući perioperativni infarkt miokarda (1,7% naspram 0,97%;  $P=0,974$ ), perioperativnu smrt (1,7% naspram 0,97%;  $P=0,974$ ) i perioperativne neurološke komplikacije kao što je moždani udar (0% naspram 0,97%;  $P=0,770$ ). Nisu zabilježene razlike u demografskim faktorima između dijabetičara i nedijabetičara. Zaključak: i pored povećane prevalencе bilateralne stenozе i periferne arterijske okluzivne bolesti kod bolesnika s dijabetesom koji su bili podvrgnuti CEA, stope perioperativnog morbiditeta, mortaliteta su bile bez statistički značajne razlike

**Ključne riječi:** simptomatska stenozа karotidne arterije, karotidna endarterektomija, dijabetes melitus

### INTRODUCTION

Cerebrovascular insult (CVI) as a consequence of carotid artery disease (stenosis, occlusion) is the third most common cause of death

in industrialized countries, the most common neurological diagnosis requiring hospitalization (1), as well as the leading cause of long-term disability (2). Carotid endarterectomy (CEA), even according to the latest guidelines, remains a recommendation and the "gold standard"

in the treatment of symptomatic carotid artery stenosis and prevention of cerebrovascular events (3-6).

Diabetes mellitus is one of the main risk factors for the development of stroke. Patients with DM compared to non-diabetic patients have two times more chance to suffer from a stroke (7). In addition, stroke in diabetic patients compared to non-diabetic patients is associated with worse functional outcome and higher mortality (8-10). Several authors have described DM as a factor that significantly influences CEA results (11-13), but there are also studies that give other results (14,15).

Moreover, in the analysis of risk factors affecting early and late outcomes in diabetic patients, there is insufficient data in the literature (16), and there is also insufficient data in the literature on the influence of DM on the early outcome of carotid endarterectomy. But, there is sufficient evidence for increased early morbidity after other vascular surgical interventions in patients with DM (17,18).

## AIM

The aim of this study was to compare early outcomes after carotid endarterectomy between diabetic and non-diabetic patients with symptomatic stenosis.

## MATERIALS AND METHODS

This retrospective study included 161 patients who underwent CEAs due to symptomatic carotid artery stenosis (stenosis > 50%), in the period from January 2018 to May 2022 at the Clinic of Cardiovascular Surgery, Clinical Center University of Sarajevo. The performed CEAs were divided into two groups: the group with DM (n=58; 36%) and the group of patients without DM (n = 103; 64%).

Our study was conducted according to the Declaration of Helsinki in 1975, written informed consent was obtained from all patients.

Patients were considered symptomatic if they had transient ischemic attacks, vertigo, amaurosis fugax, or non-disabling stroke ipsilateral to symptomatic carotid stenosis in the past 6 months. In patients with bilateral carotid stenosis, the choice of carotid artery, which was the first surgically treated, was made according to the degree of carotid stenosis.

The following data were collected for each patient: age, gender, history of hypertension (HTA), hyperlipidemia (HLP), smoking status, history of non-surgically treated coronary artery disease (CAD), history of peripheral arterial disease (PAOD), CEAs technique data (eversion/classic), type of anesthesia (local, general) and use of shunt during operative treatment. Due to the type of symptoms the following data were collected: dizziness, transient ischemic attack (TIA), amaurosis fugax non-disabling CVI. Concerning CVI, myocardial infarction (MI) and mortality were analyzed.

Patients were surgically treated under local anesthesia or, alternatively, under general anesthesia whenever local anesthesia was not feasible for patient-related reasons. CEA was performed by eversion and classical technique with patch plastic (dacron patch was used), with selective use of shunt. In patients operated under the local anesthesia, the shunt was used depending on the state of consciousness and motor functions after trial clamping of the carotid arteries, the tests to assess consciousness included counting numbers

and the motor function was tested by squeezing a squeaky rubber dummy with the contralateral hand, the carotid shunt was inserted immediately after speech or motor dysfunction. The shunt was used in patients operated in general anesthesia, in case the return pressure in the internal carotid artery after clamping was less than 40 mmHg. All patients were monitored postoperatively in the intensive care unit for at least 24 hours with strict blood pressure control (19).

The degree of stenosis was determined by Doppler ultrasound and CT angiography/MR angiography. The main sources of data were the computerized database and the standard medical histories of hospitalized patients (medical history, operating list, patient's daily therapy list, discharge letter). Anesthesiologist, vascular surgeon and neurologist participated independently in the assessment of the patients' clinical condition. For this study, patients were monitored for 30 days after surgery.

Exclusion criteria were patients with carotid artery restenosis, carotid artery stenosis with associated supra-aortic branch stenosis, carotid artery dissection, carotid artery aneurysms, simultaneous CEA surgery and aorto-coronary bypass or peripheral revascularization, and patients with asymptomatic carotid artery stenosis.

All patients were followed up for 30-day complications, such as stroke, MI and mortality. Postoperatively, neuroimaging was performed only in those patients who had a neurological deficit.

## Statistical analysis

Baseline characteristics were collected and presented as number of cases and percentage representation. Categorical values were analyzed with the  $\chi^2$  test and Fisher's test. Student's T-test and Mann-Whitney U test were used to analyze quantitative values. Statistical hypotheses were tested at the level of  $\alpha = 0.05$ , (significant if  $p < 0.05$ ). Statistical analyzes were performed using IBM SPSS Statistics ver. 21.0.

## RESULTS

In our retrospective comparative study, a total of 161 patients who underwent CEAs were included, 101 (62.7%) male and 60 (37.3%) female underwent CEAs. In 36% of cases with DM and in 64% of cases without DM CEAs was performed.

The average age of patients was 67.85 years (SD  $\pm 8.5$ , in the range from 46 to 86 years), the average age of the patients in DM group was 68.12 years (SD  $\pm 7.9$ , in the range from 53 to 86 years), while the average age in patients without DM was 67.7 years (SD  $\pm 8.8$ , in the range from 46 to 84 years,  $P=0.966$ ). Number of male was higher in both groups (60.3% vs. 64.1%) but without statistical significance,  $P=0.764$ . The preoperative risk factors and comorbidities, in the examined groups, are without statistical significance: smokers 21 (36.2%) vs 40 (38.8%),  $P= 0.872$ ; hypertension 52 (89.7%) vs 97 (94.2%),  $P=0.353$ ; hyperlipidemia 49 (84.5%) vs 87 (84.5%),  $P=0.998$ ; cardiac artery disease 17 (29.3%) vs 23 (22.3%);  $P=0.427$ . Unlike the previously mentioned variables, in the group of patients with DM the number of patients with peripheral arterial occlusive disease was higher and this difference was statistically significant (32.8% vs 16.5%,  $P=0.029^*$ ), (Table 1).

Table 1 Demographic characteristics, risk factors and comorbidities of patients with symptomatic carotid artery stenosis.

Variables	Total (n=161)	Diabetes mellitus group (n=58; 36%)	No diabetes mellitus group (n=103; 64%)	P
Age, years (SD)	67.85±8.5	68.12±7.9	67.7±8.8	0.966
Gender				0.764
Male	101 (62.7%)	35 (60.3%)	66 (64.1%)	
Female	60 (37.3%)	23 (39.7%)	37 (35.9%)	
Comorbidities				
CAD	40 (24.8%)	17 (29.3%)	23 (22.3%)	0.427
PAOD	36 (22.3%)	19 (32.8%)	17 (16.5%)	<b>0.029*</b>
Risk factor				
HTA	151 (93.7%)	52 (89.7%)	97 (94.2%)	0.353
HLP	134 (81.3%)	49 (84.5%)	87 (84.5%)	0.998
Smoking	61 (37.8%)	21 (36.2%)	40 (38.8%)	0.872

Values are presented as mean ± SD or n (%). SD: Standard deviation, CAD: Coronary artery disease; PAOD: Peripheral arterial occlusive disease; HTA- hypertension; HLP: hyperlipidemia

Analyzing the data on the preoperative status of the carotid arteries and the CEAs procedure, there was no statistically significant difference between the analyzed groups in the prevalence of contralateral occlusion 5 (8.6%) vs. 7 (6.8%), P=0.758; anesthesia technique used during the procedure (local anesthesia 74.2% vs 76.4%, general anesthesia 27.6% vs 23.3%), P=0.679; the type of

CEAs: CEAs with patch angioplasty 18 (25.3%) vs 26 (25.2%), eversion technique 40 (69%) vs 77 (74.8%), P=0.544, CEAs with a shunt 7 (12.1%) vs 8 (7.8%), P=0.536. The group with DM had a higher, statistically significant, number of patients with bilateral stenosis (31% vs 16.5%; P=0.046\*), (Table 2.)

Table 2 Preoperative and operative data.

Variables	Total (n=161)	Diabetes mellitus group (n=58; 36%)	No diabetes mellitus group (n=103; 64%)	P
Bilateral stenosis	35 (21.7%)	18 (31%)	17 (16.5%)	<b>0.046*</b>
Contralateral occlusion.	12 (7.5%)	5 (8.6%)	7 (6.8%)	0.758
CEA				
General anesthesia	40 (24.8%)	16 (27.6%)	24 (23.3%)	0.679
Local anesthesia	121 (75.2%)	42 (72.4%)	79 (76.4%)	
Use of shunt	23 (8.4%)	7 (12.1%)	8 (7.8%)	0.536
Reconstruction technique				0.544
Patch angioplasty	44 (27.3%)	18 (25.3%)	26 (25.2%)	
Eversion	117 (72.7%)	40 (69%)	77 (74.8%)	

CEA: Carotid endarterectomy

Table 3 shows the perioperative outcomes. For all patients, the 30-day rate of any type of stroke was 0.6%, MI 1.25%, while the 30-day mortality rate for all patients was 1.25%. The total percentage of observed complications in our research was 3.1%. There was no statistically significant difference between the compared groups in any type of stroke (0% vs 0.6%; P=0.770), MI (1.7% vs 0.97%; P=0.974),

and mortality (1.7% vs 0.97%; P=0.974). The percentage of total complications (morbidity and mortality) in the group of patients with DM was higher compared to the group of patients without DM, but this difference was not statistically significant (3.4% vs 2.91%; P=0.273).

Table 3 Thirty-day morbidity and mortality following CEA.

Variables	Total (161)	Within 30-day outcomes after CEA		P
		Diabetes mellitus group (n=58;36%)	No diabetes mellitus group (n=103,64%)	
CVI	1 (0.6%)	0	1 (0.97%)	0.770
IM	2 (1.25%)	1 (1.7%)	1 (0.97%)	0.974
Death	2 (1.25%)	1 (1.7%)	1 (0.97%)	0.974
Total	5 (3.1%)	2 (3.4%)	3 (2.91%)	0.835

MI myocardial infarction; CVI cerebrovascular incident

Data on the symptomatology of carotid stenosis by group is shown in Table 4. There was no statistically significant difference between the analyzed groups in the presence of dizziness (39.5% vs

45.6%; P=0.570), amaurosis fugax (18.6% vs 16.5%; P=0.858), non-disabling CVI (24.1% vs 20.4%; P=0.723), as well as in TIA as a symptom of carotid artery stenosis (19% vs 17.5%; P=0.982).

Table 4 Clinical presentation of patients with symptomatic carotid artery stenosis.

Variables	Total (161)	Diabetes mellitus group (n=58;36%)	No diabetes mellitus group (n=103;64%)	P
Vertigo	70 (43.5%)	23 (39.5%)	47(45.6%)	0.570
Amaurosis fugax	27 (17.4%)	10 (18.6%)	17 (16.5%)	0.858
CVI	35 (21.4%)	14 (24.1%)	21 (20.4%)	0.723
TIA	29 (18%)	11 (19%)	18 (17.5%)	0.982

CVI cerebrovascular incident, TIA transient ischemic attack.

## DISCUSSION

After the first CEA performed by De Bakey ME, (20), it was established as a safe and effective method to reduce the risk of CVI in patients with carotid stenosis. Today, CEAs is a method with low mortality and frequency of perioperative complications, in symptomatic (21) and asymptomatic carotid artery stenosis (22).

Stroke is one of the leading causes of death in Western countries, and the most common neurological diagnosis requiring hospitalization (1). Also, stroke has major adverse effects on a person's physical, psychological, social and economic status. Atherosclerotic disease of the carotid arteries is a disease of the elderly population group (22). In our study, patients with DM were slightly older. Our study was in accordance with others where an increased number of male was recorded (23).

In earlier studies, evaluating the relationship between DM and higher operative risk during CEAs, results are quite mixed. In previous studies, which included patients operated on for stenotic occlusive disease of the carotid arteries, the percentage of patients with DM in most cases ranged from 13 to 23.6% (24,25). Our study included 36% of patients with DM, which is significantly higher compared to the study conducted by Ahari A, et al., which had 13% of patients with DM (26). The study by Dorig W, et al., reported a percentage of patients with DM of 20.05%, while the study by Rockman CB, et al., reports 23.5% of patients with DM (24,15). Other studies, in accordance with our, reported a high percentage of diabetics, even up to 39% (27). The percentage of patients with DM in our research can be explained by the fact that in the last two decades DM has reached epidemic proportions in the general population, and especially in the group of patients with atherosclerotic disease.

Our research indicated a higher number of patients with bilateral stenosis in the group of patients with DM, with a statistically significant difference (31% vs 16.5%;  $p=0.046^*$ ). There was also a statistically significant number of patients with PAOD (32.8% vs 16.5%,  $p=0.029^*$ ).

Research by Hussain MA, et al., reported an increased risk of CVI in patients with DM, where they found that DM was associated with a 1.5-fold increased risk of stroke after CEAs (28). In our study, there was no statistically significant difference in the number of ICV, which is the same as the report of Ballota E, et al., who suggest that there is no significant difference in the frequency of these postoperative complications between patients with DM and patients without DM (16). Postoperative cardiac complications, including MI, occurred in 1.7% of patients with DM and in 0.97% of patients without DM ( $P=0.974$ ). The results of some other studies were consistent with ours, and did not indicate a significant difference in postoperative cardiac events. Altinbas A, et al. noted that after CEAs, consequent coronary insufficiency occurred in 2.3% of cases, with no observed difference between groups (29).

The total postoperative morbidity (cardiac and neurological) was present in 1.7% of patients with DM and 1.94% of non-DM patients, while mortality was higher in patients with DM 1.7% compared to non-DM patients 0.97% ( $P=0.974$ ), while total postoperative mortality and morbidity was in the group of patients with DM 3.4% and in patients without DM 2.91% ( $P=0.273$ ). Some studies reported that DM patients had higher 30-day mortality rates (3.2 vs. 1.4%;  $P=0.02$ ) (26). Overall postoperative complications were observed in 8.5% of non-diabetics and in 18.3% patients with DM ( $P<0.001$ ). Patients with DM were at more than two-fold increased risk of postoperative complications. Research by Dorigo W, et al., indicated that the risk of postoperative complications is twice as high in patients suffering from DM (24). Similar to our results, other studies concluded that patients with DM were not at greater risk of 30-day morbidity and mortality after CEAs than those without DM (27).

## CONCLUSION

Despite the increased prevalence of bilateral stenosis and peripheral arterial occlusive disease in patients with diabetes who underwent CEA, the rates of perioperative morbidity and mortality were not statistically significantly different compared to patients without diabetes.

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# Clinical significance of neutrophil to lymphocytes ratio in differential diagnosis of cervical lymphadenopathy

## Klinički značaj odnosa neutrofila i limfocita u diferencijalnoj dijagnostici cervikalne limfadenopatije

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### ABSTRACT

Introduction: cervical lymphadenopathy refers to swelling of lymph nodes in the neck and is a common presentation of various diseases. An emerging new prognostic marker, neutrophil to lymphocyte ratio, is proving to be useful in differentiating between malignant and non-malignant lymphadenopathy. Aim: to investigate whether a neutrophil to lymphocyte ratio helps with determining early the cause of cervical lymphadenopathy. Materials and methods: a retrospective case-control study was conducted at the Department of Otorhinolaryngology of the Clinical Centre University of Sarajevo. Records of patients with cervical lymphadenopathy who underwent a diagnostic excisional lymph node biopsy in a five-year period between 2016 and 2021 were retrospectively reviewed and NLR ratios were compared. Results: a total of 37 patients were reviewed and 21 patients were included and sorted into three groups: Reactive lymphadenopathy (RAL), Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). There was no statistically significant difference between the groups ( $p=0.2798$ ) in age and gender ( $p=0.8487$ ). An almost statistically significant difference was recorded between the NHL and HL groups in the obtained values of the ratio of NLR ( $p=0.073$ ). Conclusion: careful assessment of the complete blood count and differential blood count can be useful in differentiating between benign and malignant diseases. Measurement of NLR and established inflammation marker is an easy and cost-effective way of assessing the potential of malignancy in cervical lymphadenopathy. The final diagnosis should be done by excisional biopsy.

**Keywords:** neutrophil to lymphocyte ratio, cervical lymphadenopathy, malignant lymphoma, predictive marker

### INTRODUCTION

Cervical lymphadenopathy refers to swelling of lymph nodes in the neck and is a common presentation of various diseases. It occurs most frequently due to infectious processes localised in the head and neck region such as tonsillitis, otitis or dental decay (1). However, it can occasionally be a harbinger of haematological malignancies as well

### SAŽETAK

Uvod: pojam cervikalne limfadenopatije odnosi se na otok vratnih limfonoda, entitet koji se često javlja u različitim oboljenjima. Novootkriveni prognostički marker, odnos neutrofila i limfocita (NLR-neutrophil to lymphocyte ratio), može poslužiti u diferencijaciji između maligne i nemaligne limfadenopatije. Cilj: ispitati korist procjene odnosa neutrofila i limfocita u ranom određivanju uzroka cervikalne limfadenopatije. Materijali i metode: retrospektivna studija slučaja sprovedena je na Klinici za uho, grlo, nos i hirurgiju glave i vrata na Univerzitetnom Kliničkom Centru u Sarajevu. Historije pacijenata sa cervikalnom limfadenopatijom koji su podvrgnuti dijagnostičkoj ekscizionoj biopsiji limfonoda u petogodišnjem periodu od 2016. do 2021. godine retrospektivno su pregledane, a njihovi NLR su upoređivani. Rezultati: od ukupno 37 razmatranih pacijenata, 21 pacijent je uključen u studiju i pomenuti su sortirani u tri grupe: reaktivna limfadenopatija (RAL), Hodgkin limfom (HL), i non-Hodgkin limfom (NHL). Nije bilo statistički značajne razlike između grupa ( $p=0.2798$ ) po dobi i spolu ( $p=0.8487$ ). Gotovo statistički značajna razlika zabilježena je između NHL i HL grupa u dobivenim vrijednostima NLR ( $p=0.073$ ). Zaključak: pažljiva procjena kompletne krvne slike i diferencijalne krvne slike može biti korisna u diferencijaciji između benignih i malignih oboljenja. Mjerenje NLR i upalnih markera jednostavan je i isplativ način u procjenjivanju potencijalnih maligniteta u cervikalnoj limfadenopatiji. Završna dijagnostika bi svakako trebala biti izvršena ekscizionom biopsijom.

**Ključne riječi:** odnos neutrofila i limfocita, cervikalna limfadenopatija, maligni limfom, prediktivni marker

as chronic inflammatory conditions. It is reasonable that lymphoma is frequently identified in the neck because the head and neck area contain a dense lymphatic system and around one-third of the body's lymph nodes. Due to the extreme opposing severity of these two diagnoses it is crucial to attempt a prompt differentiation.

The clinicians are then faced with a choice: either to follow up the patient or to perform a biopsy. In case of evaluation via follow up, the diagnosis of lymphoma may be delayed, while an open biopsy is

associated with surgical risks and costs. Methods such as ultrasound, MRI, PET/CT, and biopsy are frequently used to consolidate a diagnosis. However, an emerging new prognostic marker - neutrophil to lymphocyte ratio - is proving to be useful in differentiating between malignant and non-malignant conditions (2).

The neutrophil to lymphocyte ratio (NLR) is a powerful predictive marker for patients with a variety of illnesses (3). The innate immune response, which is primarily supported by neutrophils, and adaptive immunity, supported by lymphocytes, is combined in the neutrophil-to-lymphocyte ratio (NLR), which is determined as a simple and direct ratio between the counts of neutrophils and lymphocytes in peripheral blood. A recent study by Song M, et al. indicates that NLR could also forecast overall population mortality (4). NLR's prognostic significance in many solid tumours is evident; it is still ambiguous in leukemias and lymphomas. Therefore, the aim of this study was to determine effectiveness of predictive markers, specifically NLR, as well as the neutrophil and lymphocyte counts in establishing a diagnosis of lymphoma versus reactive lymphadenopathy.

## AIM

The aim of the paper was to investigate whether a neutrophil to lymphocyte ratio helps in early differentiation of the cause of cervical lymphadenopathy. Prompt diagnosis is vital for a successful treatment.

## MATERIALS AND METHODS

### Study design

This retrospective case-control study was conducted at the Department of Otorhinolaryngology of the Clinical Centre University of Sarajevo. Records of patients with cervical lymphadenopathy who underwent a diagnostic excisional lymph node biopsy in a five-year period, between 2016 and 2021, were retrospectively reviewed. A total of 37 patients who underwent cervical lymph node biopsy were reviewed and 21 patients were included and sorted into three groups: Reactive lymphadenopathy (RAL), Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL).

A questionnaire was developed and demographic data, medical history and blood count were ascertained from the said questionnaire. Data on age, gender, complete blood count, and NLR in the HL, NHL and RAL groups were added into a data base and

compared via statistical analysis. The NLR was calculated by dividing the number of neutrophils with the number of lymphocytes.

Majority of patients were at least 18 years of age, with the exception of two children aged 10 and 2, with no etiological cause by history and they underwent a complete ear, nose, and throat examination, as well as ultrasound of the suspect lymph node. Blood samples of the patients were retrieved from the peripheral veins on admission. Histopathological preparations of all patients were evaluated at the Department of pathology of the Clinical Centre University of Sarajevo.

### Statistical analysis

The study was conducted in accordance with the principles of the Helsinki Declaration. Statistical analysis was done in MedCalc Statistical Software version 19.0.3. (MedCalc Software bvba, Ostend, Belgium). The D'Agostino - Pearson test was applied to assess the distribution of the results. Descriptive data are presented in frequencies (n) and percentages (%) for categorical variables and mean (median) value with interquartile range (IQR) for numerical variables that did not have a normal distribution. Chi-square test was applied for comparison of categorical variables, Kruskal Wallis test for comparison of numerical variables between groups. The non-parametric Mann-Whitney test was used to analyze differences between groups, and Dunn's post-hoc test was used for post-hoc pairwise comparisons between the groups. Values of  $p < 0.05$  were considered statistically significant.

## RESULTS

### Demographic characteristics

Out of the total number of patients included in the study 21 had RAL, HL, or NHL. The remaining 16 had unusual presentations, and as such were excluded during the final analysis. These patients were divided into three groups, reactive lymphadenopathy (RAL), Hodgkin Lymphoma (HL) and non-Hodgkin lymphoma. The median age of patients in the RAL group was 38 years, in the NHL group 51 and in the HL group 43 years. There was no statistically significant difference between the groups ( $p=0.2798$ ). There was no statistically significant difference in the distribution of patients by gender ( $p=0.8487$ ), which can be observed in Table 1.

Table 1 Demographic data.

Variable	RAL (n=9)	NHL (n=8)	HL (n=4)	p
Age median (IQR)	38,0 (22-65)	51 (47,25-68)	43,5 (33,25-53,5)	0,2798*
Sex, n (%)				0,8487**
Females	3 (33%)	3 (37,5%)	2 (50%)	
Males	6 (67%)	5 (62,5%)	2 (50%)	

\*Kruskal-Wallis test applied \*\*Chi square test applied

Table 2 Haematologic findings.

Variable	Median (IQR)	Median (IQR)	Median (IQR)	p*
	RAL (n=9)	NHL (n=8)	HL (n=4)	
Leukocytes $\times 10^3 \mu\text{L}$ (3.4-9.7)	7.4 (6.5-8.2)	6.4 (6.1-7.5)	9.9 (9.1-11.35)	0.069
Neutrophils $\times 10^3 \mu\text{L}$ (1.8-7.8; 44-72%,)	4.1 (3.3-5.0)	3.97 (3.1-4.5)	7.4 (7.2-7.6)	0.024
Lymphocytes $\times 10^3 \mu\text{L}$ (0.8-4.6; 20-46%)	1.95 (1.4-3.0)	1.7 (1.2-2.8)	1.7 (0.97-2.6)	0.780
Thrombocytes $\times 10^3 \mu\text{L}$ (158-424)	277 (210-344)	203 (174.8-237.5)	288.5 (258.5-317.5)	0.133
MPV fl (6.8-10.4)	7.7 (7.0-8.7)	8.2 (7.2-9.6)	7.8 (7.29-7.85)	0.695
NLR	1.72 (1.35-4.01)	1.85 (1.37-3,20)	4.54 (2.92-8.97)	0.138
PLR	145.5 (91.0-170.2)	112.6 (73.6-138.8)	157.2 (112.2-326.8)	0.439

\* Kruskal-Wallis test applied

The mean number of leukocytes was  $7.4 \times 10^3 \mu\text{L}$  in the RAL group,  $6.4 \times 10^3 \mu\text{L}$  in the NHL group, and  $9.9 \times 10^3 \mu\text{L}$  in the HL group. The difference in the number of leukocytes was not statistically significant ( $p=0.069$ ). The mean number of neutrophils in the RAL group was  $4.1 \times 10^3 \mu\text{L}$ ,  $3.97 \times 10^3 \mu\text{L}$  in the NHL group, and  $7.4 \times 10^3 \mu\text{L}$  in the HL group. In Table 2, the difference between the groups in the number of neutrophils is visible; and is shown to be statistically significant ( $p=0.024$ ). The mean number of lymphocytes in the RAL group was  $1.95 \times 10^3 \mu\text{L}$ ,  $1.7 \times 10^3 \mu\text{L}$  in the NHL group, and  $1.7 \times 10^3 \mu\text{L}$  and  $1.7 \times 10^3 \mu\text{L}$  in the HL group. The difference between the groups in the number of lymphocytes was not statistically significant ( $p=0.780$ ). The mean platelet count in the RAL group was  $277 \times 10^3 \mu\text{L}$ ,  $203 \times 10^3 \mu\text{L}$  in the NHL group, and  $288.5 \times 10^3 \mu\text{L}$  in the HL group. The difference between the groups in the

number of platelets was not statistically significant ( $p=0.133$ ). The mean values of the average volume of platelets in the RAL group were 7.7 fl, in the NHL group 8.2 fl and 7.8 fl in the HL group. The difference between the groups in the average platelet volume was not statistically significant ( $p=0.695$ ) (Table 2).

The mean values of neutrophil to lymphocyte ratio (NLR) in the RAL group were 1.72, 1.85 in the NHL group and 4.54 in the HL group. The difference between the groups in the ratio of neutrophils to lymphocytes was not statistically significant ( $p=0.138$ ). The mean values of platelet-lymphocyte ratio (PLR) in the RAL group were 145.5, 112.6 in the NHL group and 157.2 in the HL group. The difference between groups in the ratio of neutrophils to lymphocytes was not statistically significant ( $p=0.439$ ) (Table 2).

Table 3 Haematological variables.

Variable	p***		
	RAL:NHL	RAL:HL	NHL:HL
Leukocytes $\times 10^3 \mu\text{L}$ (3.4-9.7)	0.441	0.031	0.073
Neutrophils $\times 10^3 \mu\text{L}$ (1.8-7.8; 44-72%,)	0.743	0.034	0.004
Lymphocytes $\times 10^3 \mu\text{L}$ (0.8-4.6; 20-46%, )	0.673	0.604	0.808
Thrombocytes $\times 10^3 \mu\text{L}$ (158-424)	0.139	0.825	0.073
MPV fl (6.8-10,4)	0.672	0.782	0.305
NLR	0.815	0.106	0.073
PLR	0.606	0.414	0.283

\*\*\* Mann-Whitney test applied

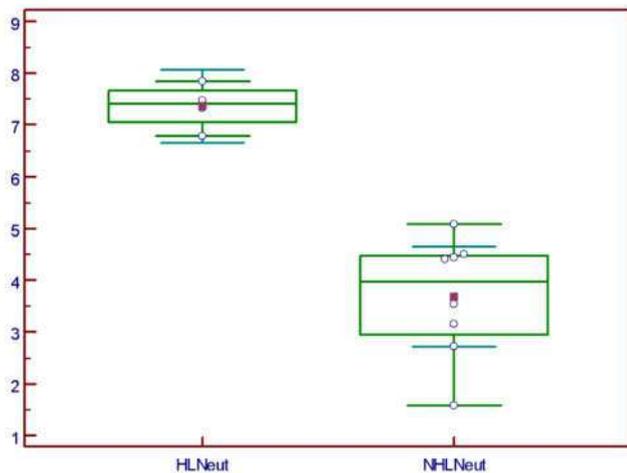


Figure 1 Neutrophil count HL and NHL.

In the pairwise comparison of the obtained results, statistically significant differences were recorded in the number of leukocytes between the RAL and HL groups ( $p=0.031$ ), similar differences were recorded in the number of neutrophils between the RAL and HL groups ( $p=0.034$ ) as well as between the NHL and HL groups ( $p=0.004$ ). It is particularly important to emphasize that an almost statistically significant difference was recorded between the NHL and HL groups in the obtained values of the ratio of neutrophils to lymphocytes NLR ( $p=0.073$ ) (Table 3, Figure 2).

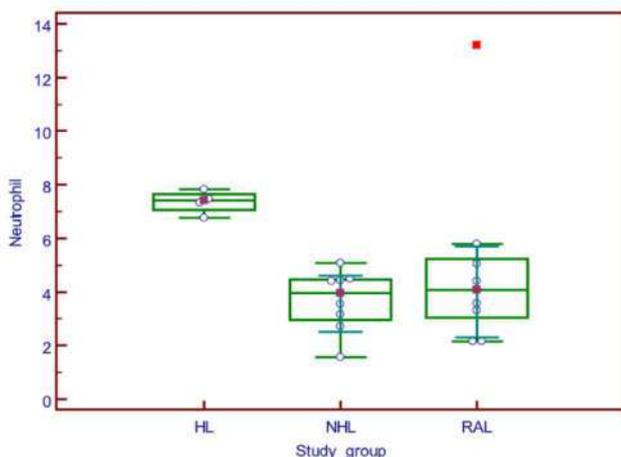


Figure 2 Neutrophil count comparison in the groups.

## DISCUSSION

As discussed earlier, role of systemic inflammation in malignancies is irrefutable (5,6). Neutrophils play a major role in inflammation in pathologic conditions such as microbial infection, chronic tissue damage, and most importantly cancer. There is also evidence that neutrophils, which are the vital components of cancer-related inflammation, have a role in tumor progression and metastasis development (7,8). Thus, a higher increase in circulating neutrophils, in combination with other diagnostic methods, is suggestive of malignancy. This is also supported by our findings as the number of

neutrophils was highest in the HL group, and there was statistically significant difference between the groups.

Lymphocytes produce adaptive immune responses to eradicate particular infections, infected cells, and occasionally precancerous or cancerous cells. Furthermore, it has been demonstrated that lymphocytes, as opposed to neutrophils, inhibit inflammation and tumor growth in the microenvironment of tumor tissue (9). However, our data did not indicate a statistically significant difference between the number of lymphocytes in the three groups.

NLR, which can be an indicator for both an increased neutrophil count and suppressed lymphocytes, are thought to show the balance between pro-inflammatory status and anti-tumor immunity. Under physiologic stress, the number of neutrophils increases, while the number of lymphocytes decreases (10,11). The NLR is a combination of both of these changes, making it more sensitive than either alone. Interestingly, our study showed an almost significant difference in the NLR ratio between the groups, and a significant difference in the sole number of neutrophils.

The prognostic value of NLR, which is one of the indicators of systemic inflammation, in many cancer types and hematological malignancies, especially lymphoma subtypes, has been validated (12). The physiologic range of NLR is between 1-2, with values below 0.7 and higher than 3 are suggestive of disease. Forget P, et al., in a large retrospective case-control study, noted that normal NLR values in an adult, non-geriatric population in good health may be between 0.78 and 3.53 (13). However, the cut off point for NLR is still debated as the range between 2.3 and 3 represents a grey zone.

Karakonstantis S, et al., observed numerous factors that could cause a "false" increase in NLR (14). These factors were age, exogenous steroid intake, sexual hormones, active haematological diseases, such as leukemia, cytotoxic drugs, obesity, diabetes, and even emotional stress. Therefore, it is self-evident that NLR cannot be used as the sole factor in differentiating inflammation from malignancy.

Limits of the study were a relatively low number of participants, as the complete number of patients coming to the clinic for cervical lymphadenopathy could not be taken in account. This is due to the fact that number of patients had unusual and rare presentations of diseases such as metastasis of urothelial carcinoma, Whipple disease and tuberculosis of lymph nodes. Our study did not correct for confounding factors mentioned above given that full patient history was sometimes unavailable. Assessing the dynamics of the white blood cell count during the disease period could be of interest for further research (15).

## CONCLUSION

Careful assessment of the complete blood count and differential blood count can be useful in differentiating between benign and malignant diseases. Measurement of NLR and established inflammation marker is an easy and cost-effective way of assessing the potential of malignancy in cervical lymphadenopathy. The final diagnosis should be done by excisional biopsy. However, it is important to note major confounding factors such as age, sex, chemotherapy, and hematologic disease.

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# Comparison of efficacy of femoral AO/OTA 31-A2 intertrochanteric fractures treated with dynamic hip screw (DHS) and proximal femoral nail (PFNA)

## Učinkovitost osteosinteze intertrohanternih AO/OTA 31-A2 preloma femura tretiranih sa dinamičkim vijkom (DHS) u odnosu na intramedularnu fiksaciju (PFNA)

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### ABSTRACT

Introduction: surgical treatment of intertrochanteric fractures consists of intramedullary and extramedullary fixation. Aim: to compare intramedullary and extramedullary osteosynthesis in stable intertrochanteric AO/OTA 31-A2 fractures treated with intramedullary nail (PFNA) or dynamic screw plate (DHS). Materials and methods: the study included 80 patients with verified AO/OTA 31-A2 fracture. After satisfying the inclusive factors were randomized into two groups, intraoperative and postoperative variables were noted. The Harris score was used to assess functional status. Results: the operative treatment time in the PFNA group was 40.50 min  $\pm$  10.87 while in the DHS group the average operative treatment duration was 48.50 min  $\pm$  9.21 (p=0.031). In the PFNA group, there was 270.92 ml of blood in the drain, while in the DHS group there were 380.53 ml (p=0.003). A total of postoperatively administered blood transfusions were performed in 7 patients (two blood doses) in the PFNA group, while in the DHS group a total of 15 patients received two blood doses (p=0.003). The total number of hospitalization days in the PFNA group was 10.125 and in the DHS group it was 12.787 (p=0.023). In the postoperative course, patients treated with nail had a dosed support of 40.87  $\pm$  4.35 days and patients treated with DHS for 60.42  $\pm$  3.48 days, (p=0.002). Fracture consolidation occurred in the PFNA group in 88.02  $\pm$  1.58 days and in the DHS group in 104  $\pm$  8.71 days (p=0.007). There was a difference in the Hip Harris score between the two groups three months after surgery (p<0.05) and six months after surgery there was not difference (p<0.05). Conclusion: both methods can be used in stable intertrochanteric fractures, although intramedullary fixation has been shown to be better due to shorter hospital stays, less need for transfusions, and faster rehabilitation.

**Keywords:** intertrochanteric fractures, DHS, PFNA

### SAŽETAK

Uvod: operativni tretman intertrohanternih preloma čine intramedularna i ekstramedularna fiksacija. Cilj: uporediti intramedularnu i ekstramedularnu osteosintezu kod stabilnih intertrohanternih preloma AO/OTA 31-A2 tretiranih sa intramedularnim čavлом (PFNA) odnosno pločicom sa dinamičkim vijkom (DHS). Materijali i metode: u istraživanje je uključeno 80 ispitanika sa verifikovanim AO/OTA 31-A2 prelomom. Randomizacijski su podijeljeni u dvije skupine, zabilježene su intraoperativne i postoperativne varijable. Harris skor je korišten za procjenu funkcionalnog stanja. Rezultati: vrijeme operativnog tretmana u PFNA grupi je bilo 40,50min  $\pm$  10,87 dok je u DHS grupi prosječno vrijeme trajanja operativnog tretmana bilo 48,50min  $\pm$  9,21 (p=0,031). U PFNA grupi u drenu je bilo 270,92 ml krvi dok u DHS grupi je bilo 380,53ml (p=0,003). Ukupno postoperativno ordinirane transfuzije krvi je bilo kod 7 ispitanika (dvije doze krvi) u PFNA grupi dok u DHS grupi ukupno 15 ispitanika je primilo po dvije doze krvi (p=0,003). Ukupan broj dana hospitalizacije u PFNA grupi je bio 10,125 a u DHS grupi je bio 12,787 (p=0,023). U postoperativnom toku ispitanici tretirani sa čavлом su imali dozirani oslonac 40,87  $\pm$  4,35 dana a ispitanici tretirani sa DHS-om 60,42  $\pm$  3,48 dana, (p=0,002). Do konsolidacije preloma je u PFNA grupi došlo za 88,02  $\pm$  1,58 dana a u DHS grupi za 104  $\pm$  8,71 dana (p=0,007). Razlika je bila i u Harris skor u između dvije skupine tri mjeseca (p<0,05) ali nije šest mjeseci od operacije (p>0,05). Zaključak: obje metode se mogu koristiti kod stabilnih intertrohanternih preloma, mada intramedularna fiksacija se pokazala boljom zbog kraće hospitalizacije, manje potrebe za transfuzijom i bržom rehabilitacijom.

**Cljučne riječi:** intertrohanterni prelomi, DHS, PFNA

## INTRODUCTION

Intertrochanteric fractures of the femur are common injuries, most often caused by a fall (1) and are constantly increasing, taking into account that the life expectancy of the world's population has significantly increased in recent decades (2). In younger people, the most common cause of this type of fracture is the action of strong force, such as traffic accidents, falling from a great height (3). In general, intertrochanteric fractures belong to the group of fractures of the proximal end of the femur that can be intracapsular and extracapsular. Extracapsular fractures include trochanteric fractures, which are divided into: intertrochanteric, pertrochanteric and subtrochanteric (4). Given that the world's population is living a longer life, the number of such fractures is increasing, which is a great burden on the health and economic sector. In general, fractures of the proximal femur are among the top ten causes of disability (5). The goal of treatment is the earliest possible surgical treatment with an adequate type of osteosynthesis, which will enable the earliest possible verticalization and training for activities that the patient had before the injury (6,7). The type of surgical treatment directly depends on the type of fracture and its stability (8). The use of a dynamic screw plate (DHS) as well as a proximal femoral nail (PFNA) are the methods of choice in stable fractures and we consider it important to compare these two methods in AO/OTA 31 -A2. The aim of this study was to compare the functional outcome in patients with stable AO/OTA 31 -A2 femoral fractures treated with two different methods (DHS vs. PFNA - extramedullary vs. intramedullary osteosynthesis). The null hypothesis of the research is that intramedullary fixation of stable intertrochanteric fractures is more efficient in relation to stabilization with a plate and a dynamic screw.

## MATERIALS AND METHODS

An analysis of 80 patients with verified AO/OTA 31 -A2 femoral fractures treated with a dynamic screw plate (DHS) or a short proximal femoral nail PFNA (SuperNail GT) was performed. Criteria for inclusion in the study: (1) adult patients, (2) X-ray or CT verified AO/OTA 31 - A2 femoral fracture, (3) patients who walked independently before the injury. Exclusion criteria in the study: (1) pathological fractures, (2) multiple trauma, (3) metabolic diseases, (4) open fractures, (5) poor general condition, (6) periprosthetic fractures. Patients were divided into two groups. The first group consists of 40 patients treated with DHS and the second group comprised 40 patients treated with multiple SuperNail GT (PFNA). Upon admission, all patients were prescribed thromboprophylaxis (Enoxaparin) and the necessary preoperative preparation was performed. After preoperative preparation and antibiotic therapy (cefazolin) all patients were operated by the same operative team with a standardized operative technique, in the supine position. Patients treated with DHS had plate with four diaphysical screws and a dynamic screw I30<sup>0</sup> while a group of patients treated with an intramedullary nail was used a short SuperNail GT I30<sup>0</sup> with a closed fracture reposition. Drains were placed in all patients and removed on the second postoperative day. On the first postoperative day, all patients began rehabilitation, in the morning exercises for extension and flexion in the hip and knee, and then verticalization with crutches under the supervision of a physiatrist and therapist. Intraoperative and postoperative complications were noted in both groups. The first control of the patients was four weeks after the operative treatment when the control X-ray was done. The next controls were two

months, three months and six months from the operation when the final observation of the patients was made.

## AIM

The aim of this research was to compare intramedullary and extramedullary osteosynthesis in stable intertrochanteric AO/OTA 31 -A2 fractures treated with intramedullary nail (PFNA) or dynamic screw plate (DHS).

## RESULTS

In the group of patients treated with proximal femoral nails, there were a total of 18 men and 22 women with an average age 75.05. In the group of patients treated with DHS there were 20 men and the same number of women and the average age was 72.30 ( $p=0.784$ ). Also, the average height of the patients treated with the nail was 176.05 cm while their weight was 78.85 kg. In the group of patients treated with DHS the average height was 177.45 cm and the weight was 82.81 kg (Table 1), there was no statistically significant difference in the above data ( $p=0.684$ ).

Table 1 Demographic data.

	PFNA (n=40)	DHS (n=40)	
Age	75.05	72.30	$p>0.05$
Sex (m:f)	18:22	20:20	$p>0.05$
Height (m)	176.05	177.45	$p>0.05$
Weight (kg)	78.85	82.81	$p>0.05$
Hip (left:right)	16:24	21:19	$p>0.05$

The operative treatment time in the PFNA group was 40.50 min  $\pm$  10.87, while in the DHS group the average duration of operative treatment was 48.50 min  $\pm$  9.21 ( $p=0.031$ ). In all patients, the drain was placed under the fascia which was removed on the second postoperative day. The length of the incision in the group of patients treated with the nail was 8.15  $\pm$  1.88cm compared to the group treated with the plate where the length of the incision was 16.80  $\pm$  2.55cm ( $p=0.001$ ). In the PFNA group, there was 270.92ml of blood in the drain, while in the DHS group there were 380.53ml ( $p=0.003$ ). A total of postoperatively administered blood transfusions were in 7 patients (two blood doses) in the PFNA group while in the DHS group a total of 15 patients received two blood doses each, which was a significant difference ( $p=0.003$ ). The number of days spent in the hospital until surgical treatment was 4.25 in the PFNA group while it was 4.92 days in the DHS group and there was no significant difference ( $F=1.87$ ,  $p=0.120$ ). The total number of hospitalization days in the PFNA group was 10.125 and in the DHS group it was 12.787 ( $p=0.023$ ). In the postoperative course, patients treated with nail had a weight bearing of 40.87  $\pm$  4.35 days and patients treated with DHS 60.42  $\pm$  3.48 days, and there is a significant difference in relation to the PFNA group ( $p = 0.002$ ). Fracture consolidation occurred in the PFNA group in 90.02  $\pm$  1.58 days and in the DHS group in 104  $\pm$  8.71 days, which is a significant difference ( $p=0.007$ ) (Table 2).

Table 2 Intraoperative and postoperative variables.

	PFNA (n=40)	DHS (n=40)
Time of surgery (min)	40.50 ±10.87	48.50±9.21 (p=0.031)
Incision (cm)	8.15± 1.88	16.80±2.55 (p=0.001)
Drain blood (ml)	270.92	380.53 (p=0.003)
Blood transfusion	7 (40)	15 (40) (p=0.003)
Time to surgery (days)	4.25	4.92 (p=0.121)
Hospitalization (days)	10.125	12.787 (p=0.023)
Weight bearing (days)	40.87 ± 4.35	60.42 ± 3.48 (p=0.002)
Fracture consolidation (days)	88.02 ± 1.58	104 ± 8.71 (p=0.007)

The total follow-up was six months and during and there were no cases of non-union in both groups. In the group of patients treated with the nail, there was no cut out, while in the DHS group there were a total of two cases of cut out, which is a significant difference (p <0.05). Reoperation was performed in both patients treated with DHS. A total of two cases of pulmonary thromboembolism (PTE) were reported in the PFNA group while one case was in the DHS group of patients. Two cases of deep vein thrombosis (DVT) were reported in the DHS group while in the PFNA group there was a total of one case of deep vein thrombosis. There was one case of superficial infection in both groups. Postoperative hematoma was noted in nine patients of the PFNA group while in the DHS group there were seven patients with postoperative hematoma. No deaths or cerebrovascular insults were reported. There were no cases of intraoperative and/or postoperative fracture of the material or bone.

Table 3 Postoperative complications.

	PFNA (n=40)	DHS (n=40)
Death rate	0	0 NS
Non union	0	0 NS
Cut out	0	2 (p<0.05)
Revision surgery	0	2 (p<0.05)
PTE	2	1 (p=0.025)
DVT	1	2 (p=0.035)
Superficial infection	1	1 NS
CVI	0	0 NS
Postop. hematoma	9	7 (p<0.05)

Three months after the operative treatment, a functional analysis was performed via the Harris score. In patients operated with intramedullary nail, an excellent result after three months was in 90% of patients and 72.5% in patients treated with DHS (p <0.05) (Table 4).

Table 4 Hip Harris score (3 months postop).

	PFNA (n=40)	DHS (n=40)
Excellent(90-100)	22	14
Good (80-89)	14	15
Fair (70-79)	3	7
Poor (<70)	1	4
Excellent and good (%)	90.0%	72.5% (p<0.05)

Six months after the operative treatment, a Harris score test was performed and it was shown that 92.5% of the patients treated with nail had an excellent and good result, while in the group of patients treated with DHS there were 80% with excellent and good results, which there was no significant difference (p> 0.05) (Table 5).

Table 5 Hip Harris score (6 months postop).

	PFNA (n=40)	DHS (n=40)
Excellent (90-100)	26	18
Good (80-89)	11	15
Fair (70-79)	3	3
Poor (<70)	0	2
Excellent and good (%)	92.5%	82.5% (p>0.05)

## DISCUSSION

In the research, a radiological and functional analysis of two types of the most commonly used methods in the stable type of fracture of the proximal end of the femur AO/OTA 31 -A2 was performed. The research aimed to gain insight into which method is more effective in terms of the number of complications, shorter hospitalizations, faster rehabilitation and faster healing of fractures. Numerous studies have been performed on the efficacy of intramedullary and extramedullary fixation of proximal femoral fractures. According to demographic data, there was no difference between the two groups. All patients underwent the necessary preoperative preparation and the mean time to surgical treatment was similar in both groups (PFNA 4.25 days; DHS 4.92 days). The duration of operative treatment was shorter in patients treated with intramedullary nail 40 minutes while in the group treated with DHS it was 48 minutes (p=0.031). According to the research of Rathva J, et al., (2018), the length of the operative treatment with DHS was 50 minutes and 35 minutes with the operative treatment with a nail (9). The length of the operative incision in the patients treated with the nail was 8 cm and in the patients treated with DHS 16cm (p=0.001). According to Huang SG, et al., (2015), the length of the operative incision in nail-treated patients was 8cm and in DHS-treated subjects 18 cm (10). Considering the blood collected in the drains postoperatively, there was a significant difference between the two groups (p=0.0017). In the group of patients treated with the nail, the total blood in the drain was 270ml and in the group of patients treated with DHS it was 380ml. According to Singh NK, et al., (2019), the total number of drains in patients treated with DHS was 207ml (11). In a study by Sharma A, et al., (2017) on 60 patients divided into two groups, in

patients treated with DHS the average amount of blood in the drain was 221ml and in patients treated with nail it was 116ml and in patients treated with nail it was 109ml ( $p < 0.01$ ) (12). A study by Rathva J, et al., (2018) showed that there was an average of 100ml of blood in the drain in patients treated with DHS and 30ml in patients treated with nail (9). According to the same study, there was a significant difference in the number of patients who received a blood transfusion postoperatively ( $p = 0.003$ ). In our study, seven nail-treated patients received a blood transfusion while fifteen DHS-treated patients received a transfusion. All patients were started to walk on the first postoperative day and were allowed partial weight bearing. There is a significant difference between the two groups with regard to the length of movement with the partial weight bearing ( $p = 0.002$ ). Patients operated with the nail were moved with partial weight bearing for 40 days and patients treated with DHS for 60 days. According to Huang SG, et al., (2017) patients treated with nail moved with partial weight bearing for 42 days and patients treated with DHS for 57 days. There was no difference between the two groups in the time spent until surgical treatment but there was a significant difference in total hospitalization ( $p = 0.023$ ) (11). In a study by Sharma A, et al., (2017) patients treated with DHS moved with partial weight bearing for 7.8 weeks and patients treated with a nail for 7.2 weeks ( $p = 0.412$ ) (12). In the group of patients treated with the nail, the hospitalization lasted a total of 10 days, while in the other group it lasted 14 days. In a study by Muller, et al. (2020), there was no difference in longer hospital stays between the two groups (13). According to Sharma A, et al., (2017) the average hospitalization in patients treated with DHS was 10.1 days and in patients treated with nail 9.29 days ( $p = 0.13$ ) (12). The time elapsed until fracture consolidation was different in the two groups and represents a significant difference ( $p = 0.007$ ). Patients treated with the nail had a fully consolidated fracture 88 days after surgical treatment and patients treated with DHS 102 days after surgical treatment. According to a study by Foulongne, et al. (2009), fracture consolidation after three months was 88% in patients operated on DHS and 100% in patients operated on intramedullary nail (14). A study by Huang SG, et al., (2017) showed that it took 90 days for fracture consolidation to occur in patients treated with an intramedullary nail and 107 days in patients treated with DHS (10). Material migration (cut out) occurred in two DHS-treated patients and reoperation was performed in both ( $p < 0.05$ ). In a study by Muller F, et al., There was a difference ( $p = 0.025$ ) between the two groups in the number of material migrations in favor of subjects treated with an intramedullary nail (13). According to Foulongne e, et al., three patients that had cut-out were previously treated with DHS and none treated with intramedullary nail (14). In a study by Fu CW, et al., (2020) there was one cut out of 110 patients in the group operated on with DHS (15).

There were two cases of PTE and one case of DVT in the patients treated with the nail, while in the subjects operated with DHS there was one case of PTE and two cases of DVT. In a study by Foulongne E, et al., there was one case of thromboembolism in patients treated with DHS. According to a study by Singh, et al. (2019) conducted on 60 patients, there was one infection in patients treated with DHS. Also, a study by Sharma A, et al., (2017) on 60 patients showed that it was a superficial infection in a group of patients treated with DHS (13). In our study, there was one superficial infection in both groups. Functional outcome was measured via the Harris score, in our study three months and six months after surgical treatment. Three months after surgery in patients treated with intramedullary nail 22 had an excellent result, good 14 subjects (average 90.0%) and in patients treated with DHS

excellent results had 14 patients, 15 had good (average 72.5%) and there is a significant difference ( $p < 0.05$ ). According to Sharma A, et al., (2017), three months after surgery, the average Harris score in nail-treated patients was 47.6 and in DHS-treated patients it was 53.4 ( $p < 0.01$ ). In the same study, six months after Harris surgery, the score in nails operated on was 82.7 and in those operated on DHS 88.7 ( $p < 0.01$ ) (13). According to Rathva J, et al., (2018), three months after surgery, patients operated on with a nail had an average score of 59 and 53.76 in those operated on DHS ( $p < 0.001$ ). In the same study, six months after surgery, 92 had a score in nail surgery and 88.3 in DHS surgery ( $p < 0.001$ ) (10). A study by Huang SG, et al., (2015) on 60 patients measured Harris almost a year after surgery showed that in patients treated with intramedullary nail 20 had an excellent result, 8 good and in patients treated with DHS had an excellent result of 15 patients and good 10 respondents. According to the same study, the average excellent and good result in patients treated with intramedullary nail is 93.30% and in patients treated with DHS 70% (11). In our study, six months after surgery, patients treated with intramedullary nail 26 had an excellent result, a good 11 patients (average 92.5%) and patients treated with DHS excellent results had 18 patients, 15 had a good (average 82.5%) and there is a significant difference ( $p < 0.05$ ). However, it is important to note that the proportion of patients with an excellent and good score after six months is significant compared to the period after three months.

## CONCLUSION

Based on the results of our study, it was shown that both methods can be used in stable intertrochanteric fractures, although intramedullary fixation (PFNA) proved to be superior due to shorter hospitalization, less need for transfusion and faster rehabilitation.

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**Our contribution to the reduction of cardiovascular diseases in Bosnia and Herzegovina!**  
**Naš prilog redukciji kardiovaskularnih bolesti u Bosni i Hercegovini!**



# Prehospital time of severe trauma in Canton Sarajevo

## Prehospitalno vrijeme kod teških trauma u Kantonu Sarajevo

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### ABSTRACT

Introduction: prolonged prehospital time increases mortality and affects functional outcome of traumatised patients. It is optimal to primary treat and transport the patient during the "golden hour" what refers to a first 60 minutes from injury onset. Aim: to investigate prehospital time duration for severely traumatised patients in Canton Sarajevo and the modifiable factors that can lead to its shortening. Materials and methods: retrospective study included 155 patients with life threatening traumas (ISS  $\geq 16$ ) primarily treated and transported by emergency medical teams of the Institute of Emergency Medical Aid of Sarajevo Canton and accepted to the Clinic of Emergency Medicine of the CCUS during a one-year period. Results: A majority (89.03%) of patients were treated and transported to the hospital within the „golden hour“ (median time 29 minutes). Time needed to reach the scene of the accident, on scene and for transport to the hospital had median values 6, 10 and 12 minutes, respectively. ISS value very weakly positively correlated with total prehospital time (Spearman coefficient 0.17,  $p=0.038$ ). There was no significant difference in prehospital time length between polytraumas and monotraumas ( $p>0.05$ ), but there was a significant difference in relation to the mechanism of injury ( $p<0.05$ ). Puncture and gunshot wounds required the shortest and falls the longest time (median time 23 and 32 minutes, respectively). Conclusion: Total prehospital time of severely traumatised patients in the Canton Sarajevo can be considered satisfactory with a majority being treated within the „golden hour“. This heavily depends on the territorial distance between the accident location and the hospital and injury mechanism, but does not depend on the severity of injuries. Advancing traffic infrastructure and regulation as well as implementing means of trauma prevention can greatly contribute to the further decrease in total prehospital time.

**Keywords:** golden hour; total prehospital time, severe trauma

### INTRODUCTION

The goal of the emergency physicians work day is to quickly and correctly manage patients. Time is a very important factor, especially in heavily traumatised patients. Total prehospital time duration and possibilities of its shortening but also improving quality of care for the patients during this period are points of particular concern. The term „golden hour“ in trauma patients refers to the first 60 minutes from

### SAŽETAK

Uvod: produženje prehospitalnog vremena povećava mortalitet i smanjuje funkcionalni ishod kod traumatiziranih pacijenata. Optimalno je primarno zbrinuti i transportovati pacijenta u okviru "zlatnog sata" što se odnosi na prvih 60 minuta nakon povrede. Cilj: ispitati trajanje prehospitalnog zbrinjavanja u Kantonu Sarajevo za teško traumatizirane pacijente te faktore čija modifikacija može rezultirati njegovim skraćanjem. Materijali i metode: retrospektivna studija uključila je 155 pacijenata sa životno ugrožavajućim povredama koji su u toku jedne godine primarno zbrinuti i transportovani od strane Zavoda za hitnu medicinsku pomoć Kantona Sarajevo na Kliniku urgentne medicine Kliničkog Centra Univerziteta u Sarajevu. Rezultati: većina (89,03%) pacijenata je primarno zbrinuta i transportovana u hospitalnu ustanovu u okviru "zlatnog sata" (medijan 29 minuta). Vrijeme odlaska na mjesto povrede, vrijeme na mjestu povrede i vrijeme transporta imali su medijan 6, 10 i 12 minuta respektivno. ISS vrijednost je veoma slabo pozitivno korelirala sa prehospitalnim vremenom (Spearmanov koeficijent 0,17,  $p=0,038$ ). Nije bilo signifikantne razlike u trajanju ukupnog prehospitalnog vremena između pacijenata sa politraumom i monotraumom ( $p>0,05$ ) ali je bila signifikantna razlika u odnosu na mehanizme povrede ( $p<0,05$ ). Najkraće je bilo kod uboda i povreda vatrenim oružjem a najduže kod padova (medijan 23 i 32 minute respektivno). Zaključak: ukupno prehospitalno vrijeme kod pacijenata sa teškom traumom u Kantonu Sarajevo je zadovoljavajuće a kod velike većine pacijenata se uklapa u „zlatni sat“. Ovisi o teritorijalnoj udaljenosti mjesta povrede od hospitalne ustanove te mehanizmu povrede, ali ne ovisi o težini povreda. Poboljšanje saobraćajne infrastrukture i politike te uključivanje i provođenje mjera prevencije traume mogu znatno uticati na skraćenje prehospitalnog vremena zbrinjavanja.

**Ključne riječi:** zlatni sat, ukupno prehospitalno vrijeme, teška trauma

injury onset up to the time that definitive hospital treatment should commence (1). During this time frame, it is necessary to recognize and treat the „ABCDE“ priorities as identified by Advanced Trauma Life Support (ATLS) guidelines and transport the patient to the appropriate hospital (2).

Clinical experience tells us that time is of the essence in the heavily traumatised patient and authors of a limited number of

studies carried out on this subject agree that it should be as short as possible and prompt (3,4).

Most of the studies have shown that prolonged transport time increases hospital mortality and affects functional outcome (5,6). Contradictory results authors attributed to the evolution in organization of emergency medical services as well as the additional effort of these services to tend to critically ill earlier than those less in need (7). It has also been shown that the influence of prehospital treatment on mortality differs based on the types of injuries and affected regions and organ systems (8,9).

Shortening prehospital time, as useful as it is, should not be imperative if it lowers the quality of care provided to patients or if done at the expense of means of initial care (8). Also, the safety of medical staff and other road traffic participants should not be brought into danger during excessively fast driving. Correctly trained medical teams, being mindful of safety and patient care quality as well as some general system solutions, could be factors which contribute to this aim.

This study focused on critically ill trauma patients in Canton Sarajevo. The Clinic of Emergency Medicine of the CCUS is the referent tertiary care facility specialised in the acceptance and treatment of these kinds of patients. Most patients in Canton Sarajevo are initially treated and transported to this clinic by physician led emergency medical teams of the Institute for Emergency Medical Aid of Sarajevo Canton.

## AIM

The aim of this study was to investigate prehospital time duration for severely traumatised patients in Canton Sarajevo. This concretely means to investigate whether the current organisation of the Institute for Emergency Medical Aid of Sarajevo Canton met the criteria for transporting patients to a tertiary care facility within the „golden hour“. Another goal was to investigate factors which contribute to total prehospital time length and identify the possibility of modifications with the goal of shortening this time frame.

## MATERIALS AND METHODS

This research was carried out retrospectively and included 155 patients with life threatening traumas primarily treated and transported by emergency medical teams of the Institute of Emergency Medical Aid of Sarajevo Canton and accepted to the Clinic of Emergency Medicine of CCUS during a one-year period. Inclusion criteria was an Injury Severity Score (ISS)  $\geq 16$  and patients primarily treated at the scene by Institute of Emergency Medical Aid of Sarajevo Canton staff.

Exclusion criteria were patients with ISS values  $\leq 16$ , patients who died before diagnostic procedures were finalised (due to the fact that an ISS score could not be assigned to such patients), as well as patients with incomplete medical documentation. Given that the CCUS is the referent emergency department for the Federation of Bosnia and Herzegovina it treats incoming patients from other cities and cantons, these patients weren't included seeing that they are usually not directly transported from the scene of the injury and therefore the golden hour cannot be estimated correctly. Patients transported with private vehicles as well as walk in patients were also excluded from the study.

Patient data collected from the hospital digital registry BIS and the patient registry and protocol documentation from Institute of Emergency Medical Aid of Sarajevo Canton included sex, age but also quality, severity and mechanism of injury. Data on call time to the

dispatch, time of arrival on scene, time on scene, time of leaving the scene and time of arrival to the hospital were also included.

Definitions:

The total prehospital time is defined as the time from the initial call regarding the injured patient to the dispatch centre of Institute of Emergency Medical Aid of Sarajevo Canton as this is the first documented time in patient medical documentation, to the time of the arrival of the patient with emergency medicine service to the Clinic. Within this time, there are three different intervals: time of dispatch to arrival on scene, time at the scene and time of transport from the scene to the hospital. The time from the patient injury to the time of call wasn't taken into account given the retrospective character of the study and inability of taking anamnestic and heteroanamnestic data from these patients and bystanders.

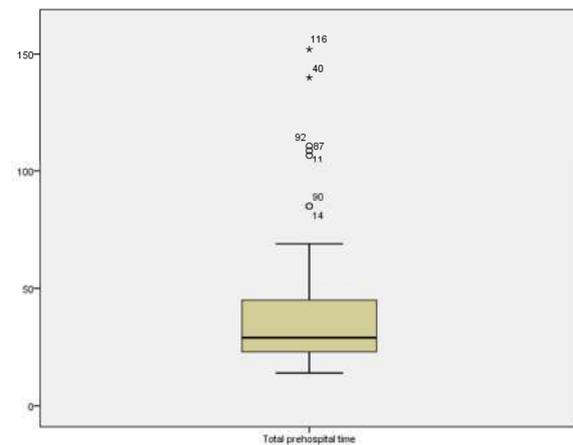
## Statistical methods

All data were calculated and graphically developed in the IBM SPSS 20 programme. The Shapiro Wilk test was used for normal distribution of continuous variables. Measures of descriptive statistics were also used: number, percentage, mean value, median and interquartile range. Data was compared using non parametric methods: Kruskal- Wallis test for multiple independent data, the Mann Whitney test for two groups of independent data, Friedman test for multiple dependent data. For the correlation we used the Spearman coefficient. A value of  $p < 0.05$  was considered statistically significant.

## RESULTS

Among the patients included in the study 80.65% were male and 19.35% were female with the average age of patients being 54.68 years (SD  $\pm 22.12$ ). The median ISS score was 25 (IQR 25-75 percentiles 20-34), with more patients fitting the criteria for polytrauma (65.8%) than monotrauma (34.19%).

The total time from the call to the dispatch regarding the injured patient up until the patient's arrival in hospital with EMS is shown in Figure 1. The mean value is 36 minutes, median 29 and interquartile range is 25.75 percentile with a confidence interval of 23-45.



Median 29 minutes, interquartile range (25-75 percentiles) 23-45  
Average value 36 minutes

Figure 1 Total prehospital time.

In a vast majority of patients (89.03%) the total prehospital time was shorter than 60 minutes, while it was prolonged in 10.97% of cases (Figure 2). The total prehospital time refers to the summation of time needed for EMS to arrive to the scene of the accident after dispatch, patient assessment and treatment on scene and time needed to transport the patient to the hospital.

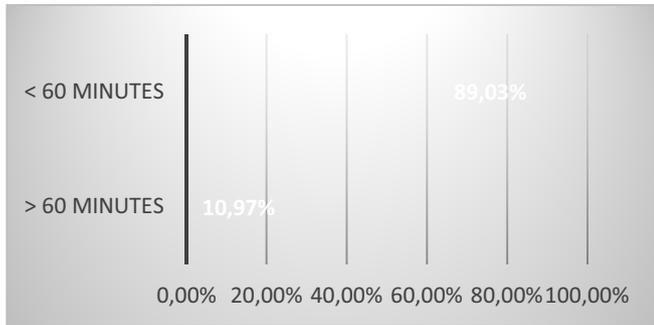
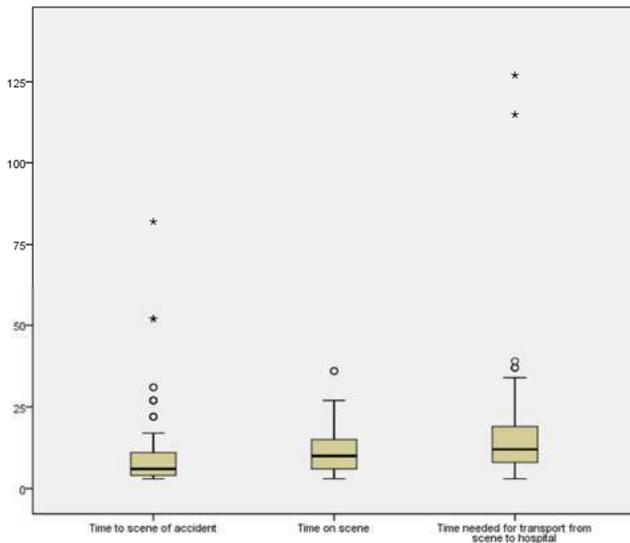


Figure 2 Ratio of patients that reached the hospital within the "golden hour".

The analysis of the lengths of these intervals has shown a statistically significant difference ( $p < 0.05$ ). Time needed to reach the scene of the accident was shown to be the shortest in our research, with a median value of 6 minutes and an average value of 9 minutes, whilst the longest time was shown to be the time taken to transport the patient to the hospital with a median value of 12 and an average value of 15 minutes (Figure 3).



Time to scene: median 6 minutes, interquartile range (25-75 percentile) 4-11, average value 9  
 Time at scene of accident: median 10 minutes, interquartile range (25-75 minutes) 6-15, average value 11  
 Time of transport from scene to hospital: median 12, interquartile range (25-75 percentile) 8-19, average value 15  
 $\chi^2 = 49.635$ ,  $P = 0.000$  (Friedman test)

Figure 3 Prehospital time intervals.

The correlation between the severity of injuries expressed by ISS value and the total amount of time from the first call to dispatch to

hospital admission is positive, statistically linear and although significant, weak as is shown in Figure 4. Spearman coefficient was 0.17 (very low),  $p = 0.038$

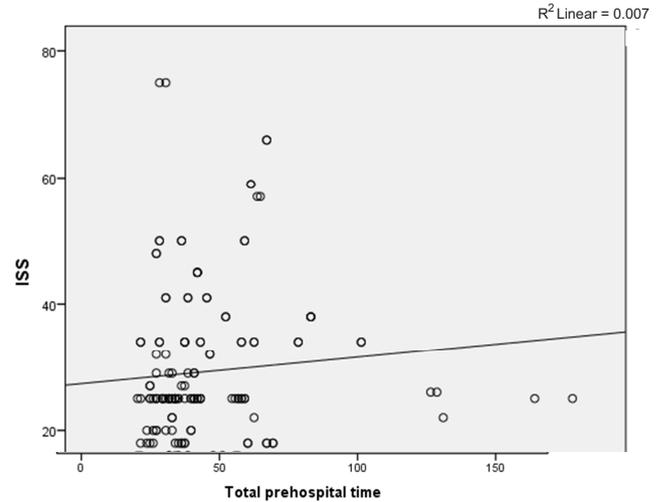


Figure 4 Correlation between ISS value and the total prehospital time.

Similarly to the individual intervals assessed, the total prehospital time did not differ in accordance to the severity of injuries, whether they were single or polytrauma (Table 1).

Table 1 The relationship between the assessed time intervals and affected organ systems.

Variables	Time to scene of accident <sup>1</sup>	Time at scene <sup>1</sup>	Time needed for transport from scene to hospital <sup>1</sup>	Time from call to dispatch until hospital admission <sup>1</sup>
Single trauma	6 (3)	7 (8)	12 (9)	27 (11)
Polytrauma	6.50 (9)	10 (11)	13 (14)	30 (26)
<sup>2</sup> P-value	0.637	0.198	0.087	0.069

<sup>1</sup> Median ( Interquartile range 25-75 percentiles)

<sup>2</sup> Mann-Whitney test

The total prehospital time shows a statistically significant difference in relation to the mechanism of the injury ( $p < 0.05$ ). There was also a statistically significant difference of time needed to reach the scene of the accident and transport duration between these groups of patients ( $p < 0.05$ ). In all of the cases assessed the shortest time intervals were in the cases of gunshot wounds. The total prehospital time was the shortest in puncture and gunshot wounds (median 23 minutes) and the longest in falls (median 32 minutes) (Table 2).

Table 2 The relationship between time intervals and injury mechanisms.

Variables	<sup>1</sup> Time to scene of accident	<sup>1</sup> Time on scene	<sup>1</sup> Duration of transport to hospital	<sup>1</sup> Time from call to dispatch until hospital admission <sup>1</sup>
Fall	6 (6)	10 (12)	14 (12)	32 (24)
Car accident	7 (9)	10 (9)	11 (15)	29.5 (20)
Physical altercation	8 (7)	7 (19)	6 (24)	28 (49)
Puncture and gun injuries	4 (4)	6 (9)	9 (5)	23 (8)
<sup>2</sup> P-value	0.022	0.236	0.024	0.02
<sup>2</sup> X <sup>2</sup>	9.639	4.249	9.478	9.791

<sup>1</sup> Median ( Interquartile range 25-75 percentiles)

<sup>2</sup> Kruskal-Wallis test

## DISCUSSION

The injuries assessed in our patients fit the criteria for major trauma and could be classified into the subgroup of very severe trauma given that the median ISS value was 25. The average age of the patients was 54.68 years and this group of patients has the highest expected mortality rate. The American College of Surgeons Committee on Trauma /ASC COT/ patients with this severity of injuries over the age of 45 have an expected mortality up to 35.37% (10). Some research have shown that the length of prehospital treatment affects the final outcome of injured patients (1,6), especially those with major trauma (5). We deemed it useful to evaluate the length of prehospital time in these patients with an already expected high mortality rate. Our research proved to be accounted for, seeing that a great majority of patients (89.03%) were treated and transported to the hospital within the „golden hour“ and the average prehospital time shorter than an hour, with a median time of 29 minutes from call to dispatch to scene arrival, length of time spent on scene and transport duration.

As already proven by previous research on this subject, territorial factors regarding the location of the accident have the most influence on the length of prehospital treatment and transport (11,12). This was also confirmed by our research with the exemption that the distance of the scene of the accident to the hospital affects the total prehospital time the most given that the median time of transport from the scene of the accident was 12 minutes. On the other hand, the median time it took for teams to arrive to the scene was only 6 minutes which is significantly less. Institute of Emergency Medical Aid of Sarajevo Canton is organised into 8 points which are territorially placed in the area of Canton Sarajevo in order to assure the shortest possible time to arrival on scene at any point in this territory, a strategic placement that has proven to be effective by the results of our study. The time-to-scene has been reduced to a minimum, proving that the organisation of this emergency service is

efficient when it comes to territorial placement. The hospitals in Canton Sarajevo are located in the city centre, meaning transport from the outskirts of the Canton can have a longer duration. However, all the ambulance teams of Institute of Emergency Medical Aid of Sarajevo Canton are physician led and equipped to provide advanced life support meaning that time in transport cannot be considered „lost time“. The problem of distance and length of transport depends tremendously on traffic infrastructure, traffic conditions and density in Canton Sarajevo.

The severity of injuries doesn't significantly influence the length of total prehospital time. The total time before hospital admission very lightly positively correlates with the ISS score and there is no significant difference in its length between single and polytrauma. Multiple organ affliction does not generate longer treatment and immobilization times before transport begins, meaning there was no significant difference in time spent on the scene between patients with injuries of one or more organ systems. In contrast to our results, the research carried out by Al Thani H, et al., showed that higher ISS scores meant longer on scene times (13). In this research, the average time spent on scene was 24 minutes which is significantly longer than the average time of 11 minutes we found. This can be attributed to the fact that these authors included all trauma patients, including those with less severe injuries who did not require such prompt action. Our results can be explained by quality EMS training leading to decreased on scene times seeing that all of the patients included in our study were suffering from life threatening injuries. Furthermore, these results were in contrast to those found by Maegele M, (14) which testified to longer on scene times (OST) in physician staffed EMS teams due to an increased number of interventions performed by these teams in comparison to paramedic only teams. This would mean that a higher count of injuries would also mean more interventions. However, it is impossible to evaluate the exact degree of injuries or exclude injuries for lack of physical findings on certain body parts before definitive hospital evaluation. For this reason, ATLS guidelines, which are considered to be the golden standard in trauma patient care, are followed in the field (15). Our results are a confirmation of the effectiveness of this protocol.

Based on the data collected in our study, we found a statistically significant difference in the duration of total prehospital time in regards to different injury mechanisms. The total prehospital time was the longest in patients hurt by falls and shortest in puncture and gunshot wounds. On scene time did not statistically differ among different injury mechanisms, unlike the time of transport. This lead to the conclusion that falls as accidents are more frequent in areas further from the centre, which results in longer durations of transport to the hospital, whilst puncture and gunshot wounds, as violent mechanism injuries, are more often seen in central city areas. This data could contribute to accurate trauma prevention complying to European and worldwide trends (10,16). Also, it would result in a decrease of heavily traumatised patients requiring prolonged prehospital treatment times.

## CONCLUSION

The average time of prehospital treatment and transport in Canton Sarajevo can be considered satisfactory, with a majority of patients being treated within the „golden hour“. This heavily depends on the territorial distance of the scene of the accident from the hospital as well as injury mechanism but doesn't depend on severity and quality of injuries. Advancing traffic infrastructure and regulation as well as implementing means of trauma prevention can greatly

contribute to the decrease in total prehospital time in trauma patients.

## LIMITATIONS

A limitation can be found in the fact that we did not record the time before call to dispatch meaning that the actual patient prehospital time is longer for this time period.

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# Segmental portal hypertension as a cause of bleeding from the upper parts of the digestive tract: case report

## Segmentalna portalna hipertenzija kao uzrok krvarenja iz gornjih partija digestivnog trakta: prikaz slučaja

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### ABSTRACT

Introduction: segmental portal hypertension (SPH) is a rare cause of bleeding from the upper parts of the digestive tract. It is most often caused by diseases of the pancreas, which with their progression lead to involvement of the splenic vein, which leads to its thrombosis. Aim: to present a case of segmental portal hypertension caused by thrombosis of the lienal vein as one of the rare causes of bleeding from the upper parts of the digestive tract. Case report: a patient admitted to the Clinic of Gastroenterohepatology of the Clinical Center University of Sarajevo due to recurrent bleeding from the upper parts of the digestive tract. A proximal endoscopy was performed, which proved varicosities in the fundic region of the stomach, without signs of acute bleeding. Then a CT scan of the abdomen with contrast was performed, which showed thrombosis of the lienal vein with consequent splenomegaly and numerous dilated perigastric collateral blood vessels. An indication for operative treatment was set, and intraoperative confirmation of clinical, endoscopic and radiological suspicion of segmental portal hypertension was obtained. A splenectomy was performed using a classical surgical technique, the postoperative course was uneventful. At the follow-up examination three months after the operation, the endoscopy showed a complete regression of the varicosities of the fundic region of the stomach, the laboratory blood findings were improving, and the clinical status was satisfactory. Conclusion: segmental portal hypertension as a cause of bleeding from the upper parts of the digestive tract should be suspected in all patients with an enlarged spleen, previous pancreatic disease, and in whom liver disease or injury has been ruled out.

**Keywords:** hemorrhage, splenomegaly, portal hypertension, splenectomy

### SAŽETAK

Uvod: segmentalna portalna hipertenzija (SPH-segmental portal hypertension) je rijedak uzrok krvarenja iz gornjih partija probavnog trakta. Najčešće je uzrokuju bolesti pankreasa koje svojom progresijom dovode do zahvatanja splenične vene što dovodi do nastanka njene tromboze. Cilj: prikazati slučaj segmentane portalne hipertenzije uzrokovan trombozom lienalne vene kao jednim od rijetkih uzroka krvarenja iz gornjih partija digestivnog trakta. Prikaz slučaja: pacijentica primljena na Kliniku za gastroenterohepatologiju Kliničkog Centra Univerziteta u Sarajevu radi recidivirajućeg krvarenja iz gornjih partija digestivnog trakta. Uradi se proksimalna endoskopija koja je dokazala varikozitete fundične regije želudca, bez znakova akutnog krvarenja. Potom se učini CT abdomena sa kontrastom koji je pokazao trombozu lienalne vene sa posljedičnom splenomegalijom i brojnim dilatiranim perigastričnim kolateralnim krvnim sudovima. Postavi se indikacija za operativni tretman, a intraoperativno se dobila potvrda kliničke, endoskopske i radiološke sumnje na segmentalnu portalnu hipertenziju. Klasičnom hirurškom tehnikom se učini splenektomija, postoperativni tok je protekao uredno. Na kontrolnom pregledu tri mjeseca nakon operacije endoskopski se dokazala potpuna regresija varikoziteta fundične regije želudca, laboratorijski nalazi krvi u poboljšanju, a klinički status zadovoljavajući. Zaključak: na segmentalnu portalnu hipertenziju kao uzrok krvarenja iz gornjih partija digestivnog trakta bi trebalo posumnjati kod svih pacijenata sa uvećanom slezenom, ranijom bolesti pankreasa, a sa isključenom bolesti ili povredom jetre.

**Ključne riječi:** krvarenje, splenomegalija, portalna, hipertenzija, splenektomija

### INTRODUCTION

Segmental portal hypertension (SPH), also known as left-sided portal hypertension, is a rare cause of bleeding from the upper parts of the digestive tract. The most common symptom that brings a

patient to the doctor is the appearance of black, tarry stools accompanied by cramping pains throughout the abdomen (1-4).

SPH differs from other forms of portal hypertension in that liver function is often preserved, and the extrahepatic part of the portal vein is intact. SPH is most often caused by diseases of the pancreas

such as acute or chronic pancreatitis, pseudocysts of the pancreas and pancreatic carcinomas, which with their progression lead to involvement of the splenic vein, which leads to its thrombosis (1-5).

Under normal anatomical and functional circumstances, venous blood is drained by the force of gravity via the short gastric arteries into the splenic vein, which at the confluence is handed over to the central portal blood flow. In the case of thrombosis of the lienal vein, arterial blood enters the spleen unimpeded via the lienal artery, while the flow of venous blood is partially or completely obstructed. In this case, due to the increased pressure in the vein segment from the hilus due to the thrombus, blood begins to move upward through the short gastric veins, opening the portocaval shunt of the gastroesophageal region. As a result of the aforementioned mechanisms, isolated fundic varicosities typical for SPH occur. The schematic view of the physiological and pathophysiological circulation caused by vein thrombosis is shown in Figure 1 (6,7).

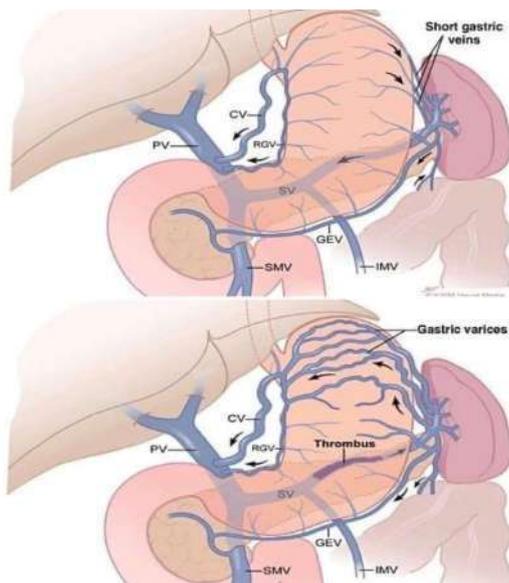


Figure 1 Physiological and pathological flow of venous blood caused by thrombosis of the lienal vein (6,7).

The treatment of choice for symptomatic patients with recurrent variceal bleeding is splenectomy, which interrupts the flow of arterial blood to the spleen and with the consequent relief of the portocaval anastomoses (5,8).

## AIM

To present a case of segmental portal hypertension caused by thrombosis of the lienal vein as one of the rare causes of bleeding from the upper parts of the digestive tract and thus draw attention to the importance of differential diagnosis in patients with splenomegaly and varicosities of the stomach in the region of the fundus, without proven primary liver disease.

## CASE REPORT

A 48 years old patient was referred to the Clinic of Gastroenterohepatology of the CCUS due to clinical and laboratory signs of acute bleeding from the upper parts of the digestive tract. Two weeks earlier, she also visited a gastroenterologist due to bleeding, which was resolved with conservative treatment.

Based on the anamnesis, it was evident that patient was previously treated for Crohn's disease when a right hemicolectomy with ileo-transverse anastomosis was performed, she underwent a gallbladder surgery and was also surgically treated for pancreatitis, but without appropriate medical documentation attached. She states that in January this year she was in a coma due to acute renal failure when she was treated for hepatorenal syndrome.

Upon admission, a clinical examination was performed, followed by esophagogastroduodenoscopy after resuscitation therapy. After removal of the coagulum, endoscopic signs of portal hypertensive gastropathy III degree with fundic varices were observed, two of which had a fibrin plug. One of them was particularly pronounced, swollen. Taking into account the duration of the procedure and the patient's general condition, the decision was made in favor of repeated conservative treatment. There were no signs of active bleeding.

A day later, a contrast enhanced computerized tomography (CT) of the abdomen was performed, which showed that the liver was in a regular position, shape and size, with a craniocaudal diameter of the right lobe up to 167 mm. The liver parenchyma was homogeneous with no signs of cirrhosis or tumor changes. The portal vein was of the appropriate width of the main stem (diameter up to 11 mm), with neat contrasting opacification and arborization. In contrast, the lienal vein did not opacify in the region of the portal vein confluence. The upper mesenteric vein was of adequate width and properly opacified with contrast along the entire course. It was a reanalyzed and extremely tortuous gastroepiploic vein filled prehilary from the lienal vein. The left gastric vein was also recanalized, which continues to the extremely dilated and tortuous perigastric venous blood vessels, which was especially pronounced near the fundus, without visible signs of active extravasation. The spleen was in an orderly position and markedly enlarged, with an interpolar diameter of up to 220 mm, and in the parenchyma of the interpolar part and towards the upper pole, wedge-shaped and mutually confluent hypodense areas of the type of stasis changes could be seen subcapsularly. The pancreas was in an orderly position, extremely gracile in shape, chronically altered, and in the area of the trunk and tail, two cystoid formations with slightly thicker walls, up to 33 and 26 mm in diameter, were recorded. As an incidental finding, it was noted that the common hepatic artery originates from the upper mesenteric artery, and the left gastric artery originates from the lienal artery. The most important details of the CT findings are shown in Figure 2.

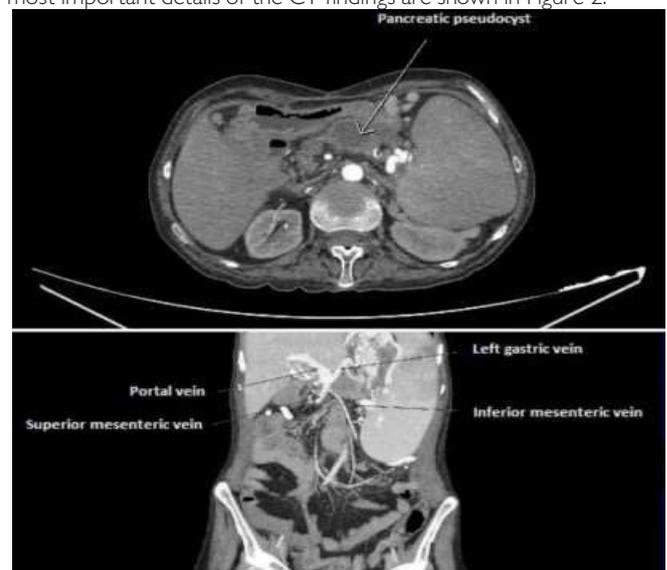
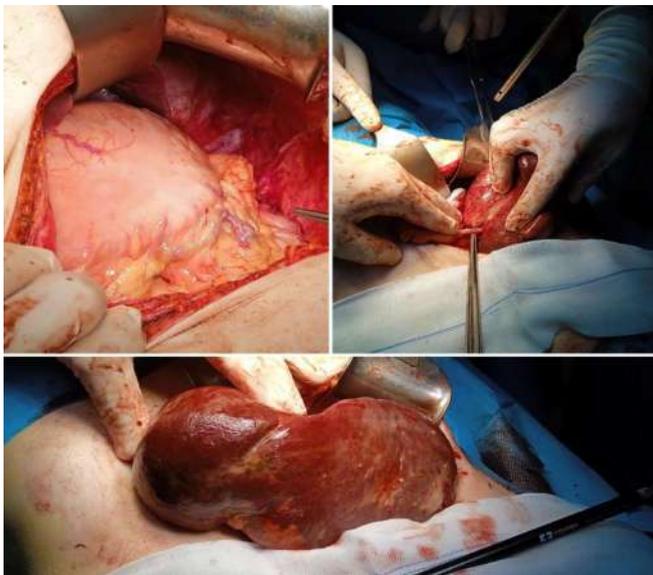


Figure 2 The most important details of CT finding.

From the gastroenterological side, primary liver disease was ruled out as the cause of bleeding in the field of portal hypertension, and an abdominal surgeon was called, who set an indication for elective surgical treatment.

Due to previous intra-abdominal procedures, we decided to perform a splenectomy using a classic open approach, where an enlarged spleen was found intraoperatively, along with extremely enlarged and tortuous venous blood vessels in the region of the hilus of the spleen and fundus of the stomach, as well as an accentuated gastroepiploic venous arcade. The spleen was freed from the surrounding adhesion and luxated forward and medially. The lienal artery and vein were shown. The lienal vein appeared thrombosed on palpation. Figure 2 shows the most important details of the intraoperative findings.

Afterwards, the mentioned vascular structures were cut and the spleen was completely removed from its socket. Following the application of additional hemostatic sutures in the area of the tail of the pancreas and fundus of the stomach, as well as a pair of metal clips, the hemostasis and integrity of the stomach lumen were checked. An abdominal drain was placed in the splenic cavity, the operative wound was closed, and the patient was placed postoperatively in the standard care surgical department. The spleen preparation was sent for regular PH analysis. The postoperative course went smoothly, and the complete reduction of gastric varices was confirmed by endoscopy of the upper gastrointestinal tract 3 months after the surgery.



**Figure 3** The most important details of the intraoperative finding: **A-Dilated fundic blood vessels; B-Lienal vein; C-Enlarged spleen.**

Pathohistological analysis confirmed the clinical, radiological and intraoperative picture of changes in the spleen as part of vein thrombosis. Hyalinized blood vessels were found, distended red pulp with reduced white pulp with an enlarged marginal zone and mildly noticeable sinus hyperplasia.

## DISCUSSION

SPH and generalized portal hypertension can cause upper gastrointestinal bleeding, but SPH is often associated with splenomegaly and normal liver function (9). In our case, we had a patient with splenomegaly and normal liver function, which in the available literature is considered a *sine qua non* finding in SPH. Therefore, SPH should be suspected in all patients with a normal liver, splenomegaly and acute bleeding from the upper parts of the digestive tract.

The most common cause of thrombosis of the lienal vein is chronic pancreatitis and pseudocysts of the pancreas due to close anatomical relationships (10). An increased frequency of pancreatic pathology, in the form of acute or chronic pancreatitis, was recorded in patients with inflammatory bowel disease (IBD) compared to the general population (11). Considering that our patient was treated for Crohn's disease, radiologically verified chronic pancreatitis does not surprise us, although the patient denies its previous existence, and the pains she had were attributed to the underlying disease.

CT with contrast and proximal endoscopy are the methods of choice for demonstrating SPH (12). In our patient, SPH was suspected by gastroscopy, and confirmed by CT enhanced radiological diagnostics. A detailed description of portocaval collaterals, morphological characteristics of the pancreas is given, and primary liver disease that would lead to generalized (central) portal hypertension is ruled out in the differential diagnosis. An aberrant starting point of the common hepatic artery is mentioned as an incidental finding, which is valuable information in the case of resection operative treatment due to chronic pancreatitis.

The treatment of SPH includes the surgical treatment of the underlying condition of SPH with splenectomy (13,14). With splenectomy, the blood flow to the left portal basin is cut off, and in this way the collaterals, that is, the varicosities of the fundic region, are relieved (15). Considering that the basic indication for the operative treatment of chronic pancreatitis was a chronic and unbearable pain syndrome, which our patient did not describe in the anamnesis, there was no indication for pancreatic resection, but only splenectomy (16).

In the available medical literature, it is stated that the characteristic operative finding in SPH implies dilated, tortuous vessels around the spleen and stomach. The gastroepiploic vein is particularly prominent, the liver is normal and there are no dilated blood vessels on the right side of the abdomen. Sometimes it is possible to show the site of thrombosis of the lienal vein (17). During our operative procedure, we were able to show the key characteristics of findings in SPH with palpatory identification of the site of lienal vein thrombosis (Figure 2).

Splenectomy brings numerous benefits in symptomatic patients, reduces/eliminates the risk of life-threatening bleeding, risks associated with multiple blood transfusions and removes hypersplenism, thereby correcting leukopenia and thrombocytopenia (18).

Control laboratory findings after three months showed a significant improvement in the blood count, but without complete normalization, which could be attributed to the chronic impact of Crohn's disease on the patient's condition. Although there is no clear surgical consensus on the use of prophylactic splenectomy in patients with SPH, its eventual clinical benefit can be seen from the above, while additional prospective studies are needed for a definitive opinion.

## CONCLUSION

Isolated obstruction of the lienal vein is a rare but important clinical condition that can lead to severe bleeding from the upper parts of the digestive tract. Segmental portal hypertension should be suspected as the cause of bleeding in all patients with an enlarged spleen, previous pancreatic disease, and liver disease or injury excluded.

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- **DISCUSSION**

- **CONCLUSION**
- **REFERENCES**

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Conclusion should be concise and should contain most important facts, which were obtained during investigation and its eventual clinical application, as well as the additional studies for the completed application. Affirmative and negative conclusions should be stated.

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References should follow the format of the requirements of **Vancouver rules**.

Every statement, knowledge and idea should be confirmed by reference. Each reference in the text is given its own sentence case in Arabic number in parenthesis at the end of the sentence according to the order of entering. Every further referring to the same reference, number of the first referring in the text should be stated. References are to be placed at the end of the article, and are to be numbered by ordinal numbers in the order of entering in the text (entering reference number). Journal's title is abbreviated using Index Medicus abbreviations. The names of the first six authors of each reference item should be provided, followed by "et al."

It is very important to properly design references according to instructions that may be downloaded from addresses National Library of Medicine Citing Medicine <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=citmed.TOC&depth=2>, or International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References [http://www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html).

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Ključne riječi - Key words, na našem jeziku i na engleskom, ukupno do pet riječi, navode se ispod Sažetka, odnosno Abstracta.

## SADRŽAJ

Sadržaj rada mora biti sistematično i strukturno pripremljen i podijeljen u poglavlja i to:

- **UVOD**
- **MATERIJAL I METODE**
- **REZULTATI**
- **DISKUSIJA**
- **ZAKLJUČAK**
- **LITERATURA**

## UVOD

Uvod je kratak, koncizan dio rada i u njemu se navodi svrha rada u odnosu na druge objavljene radove sa istom tematikom. Potrebno je navesti glavni problem, cilj istraživanja i/ili glavnu hipotezu koja se provjerava.

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## REZULTATI

Navode se glavni rezultati istraživanja i nivo njihove statističke značajnosti. Rezultati se prikazuju tabelarno, grafički, slikom i direktno se unose u tekst gdje im je mjesto, s rednim brojem i konciznim naslovom. Tabela treba imati najmanje dva stupca s obrazloženjem što prikazuje; slika čista i kontrastna, a grafikon jasan, s vidljivim tekstom i obrazloženjem.

## DISKUSIJA

Piše se koncizno i odnosi se prvenstveno na vlastite rezultate, a potom se nastavlja upoređivanje vlastitih rezultata s rezultatima drugih autora, pri čemu se citiranje literature navodi po važećim Vankuverskim pravilima. Diskusija se završava potvrdom zadatog cilja ili hipoteze, odnosno njihovim negiranjem.

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Treba da bude kratak, da sadrži najbitnije činjenice do kojih se došlo u radu tokom istraživanja i njihovu eventualnu kliničku primjenu, kao i potrebne dodatne studije za potpuniju aplikaciju. Obavezno navesti i afirmativne i negirajuće zaključke.

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