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The Power of the Microbiome

In the organization of the Clinical Center University of Sarajevo and the Discipline for Research and Development, the International Conference entitled "The Power of the Microbiome" was held at the Hollywood Hotel in Sarajevo on 7-8 November 2025. The conference gathered domestic and international experts from the field of immunology, infectology, pediatrics, microbiology, gastroenterology, internal medicine, abdominal and other surgical disciplines, and also experts from the field of nutrition, pharmacy and related sciences.

The aim of the conference was to discuss the increasingly complex and important role of the microbiome in health maintenance and disease development. Nowadays it is clear that the microbiota, as a complex and dynamic ecosystem, plays a key role in regulating immune responses, metabolism and neurological functions, but also in the modulation of the therapeutic response in numerous diseases - from inflammatory bowel diseases and metabolic disorders, to oncological, surgical and neurodegenerative conditions.

The conference was organized by the Organizing Committee composed of prominent clinicians and academic experts, while the Scientific Committee was in charge of creating and evaluating the scientific program, to ensure high academic and professional standards of the conference. The conference gathered a total of 680 registered participants, which testified to the exceptional interest of the professional public in this topic.

During the first day, lectures by invited domestic and international experts were held, focused on the basic biological principles of the microbiome, its role in different organ systems, and the clinical implications of dysbiosis. Special emphasis was placed on the microbiome - immune system axis, the influence of microbiota on metabolic and neurodegenerative diseases, and on modern diagnostic methods and challenges in the clinical application of scientific knowledge.

The second day of the conference included parallel panel sessions covering topics from infectology, family medicine, surgery, gastroenterology, pediatrics, gynecology, oncology and neuropsychiatry. Discussions were focused on practical clinical aspects of the microbiome, including its role in infectious diseases, rational use of antibiotics, inflammatory bowel diseases and metabolic disorders, as well as the possibilities of its modulation through probiotics, prebiotics, postbiotics, fecal microbiota transplantation and new biotherapeutic approaches, with special reference to the neonatal period and the importance of breastfeeding.

The conference entitled "The Power of the Microbiome" confirmed that the understanding of the microbiome represents one of the key challenges of modern medicine, but also an exceptional opportunity for the improvement of preventive, diagnostic and therapeutic strategies. The multidisciplinary approach, the exchange of experiences and the integration of basic and clinical sciences have clearly shown that the microbiome has become an indispensable link in modern medical thinking.

Conclusion

Nowadays, the microbiome cannot be regarded merely as an accompanying phenomenon, but also as an active regulator of health and disease. The conference opened up new questions, but also offered concrete answers and guidelines for future research and clinical practice, confirming that the medicine of the future is inevitably built on a deeper understanding of the relationship between man and his microbiome.

Additional information about the conference program is available on the official conference website. https://https://www.mocmikrobioma.ba/

Publishing Editor

An Evaluation of the Predictive Value of the Karnofsky Performance Status Score in Determining the Clinical Success of VATS Talc Pleurodesis in Patients with Malignant Pleural Effusion

Evaluacija prediktivne vrijednosti Karnofsky skale procjene općeg tjelesnog stanja u određivanju kliničkog uspjeha VATS talk pleurodeze kod pacijenata sa malignim pleuralnim izljevom

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ABSTRACT

Introduction: malignant pleural effusion (MPE) is a common complication of advanced malignancies and often signifies poor prognosis. Video-assisted thoracoscopic surgery (VATS) talc pleurodesis remains a widely used palliative procedure to prevent recurrent pleural effusions and improve quality of life (QoL). The Karnofsky Performance Status (KPS) score determines the prognostic value of pleurodesis in patients with MPE. Aim: to evaluate the predictive value of the KPS score in determining the clinical success of VATS talc pleurodesis in patients with MPE and to identify the most successful method of talc pleurodesis. Materials and methods: a retrospective observational study was conducted on 180 patients diagnosed with MPE who underwent talc pleurodesis in two years at the Clinic of Thoracic Surgery of the Clinical Center University of Sarajevo. Patients were divided in regards to the pleurodesis technique into three groups consisting of 60 patients each: VATS and pleurodesis (G1), standard thoracostomy and pleurodesis (G2), and thoracostomies with pleural catheters and pleurodesis (G3), respectively. A sclerosant of choice was talc. Data collected included demographic details, KPS in each group (before and after the procedure), with respective pleurodesis outcomes. Statistical analysis was performed using SPSS Statistics v19.0. Result: a statistically significant increase in KPS score in all three groups before and after the aforementioned procedures, as well as a statistically significant improvement in KPS score after VATS talc pleurodesis in comparison to patients in G2 and G3 group was observed. Conclusion: the KPS score is a valuable predictor of clinical success in patients undergoing talc pleurodesis for malignant pleural effusion.

Keywords: Karnofsky Performance Status, VATS, Talc Pleurodesis, Malignant Pleural Effusion

SAŽETAK

Uvod: maligni pleuralni izljev (MPE) česta je komplikacija uznapredovalih malignih bolesti i često korelira sa lošom prognozom. Pleurodeza talkom putem videoasistirane torakoskopske hirurgije (VATS) je široko prihvaćen palijativni postupak za sprječavanje rekurentnih pleuralnih izljeva i poboljšanje kvalitete života. Karnofsky skala procjene općeg tjelesnog stanja (KPS) određuje prognostičku vrijednost pleurodeze kod pacijenata sa MPE. Cilj: procijeniti prediktivnu vrijednost KPS skora u određivanju kliničkog uspjeha VATS pleurodeze talkom kod pacijenata sa MPE i utvrditi koji metod pleruodeze talkom ima najveći uspjeh. Materijali i metode: provedena je retrospektivna opservacijska studija na 180 pacijenata dijagnosticiranih sa MPE koji su podvrgnuti pleurodezi talkom tijekom dvije godine na Klinici za torakalnu kirurgiju. Pacijenti su podijeljeni u tri skupine s obzirom na tehniku pleurodeze, svaka po 60 pacijenata: VATS i pleurodeza (G1), standardna torakostomija i pleurodeza (G2) te torakostomija s pleuralnim kateterima i pleurodezom (G3). Sklerozant izbora bio je talk. Prikupljeni podaci uključivali su demografske podatke, KPS skor u svakoj skupini (prije i nakon procedure), s odgovarajućim ishodima pleurodeze. Statistička analiza provedena je korištenjem SPSS Statistics v19.0. Rezultat: evidentirano je statistički značajno povećanje KPS skora u sve tri skupine pacijenata prije i nakon procedure, kao i statistički značajno poboljšanje KPS skora nakon procedure između pacijenata tretiranih VATS talk pleurodezom sa jedne, te G2 i G3 skupine pacijenata sa druge strane. Zaključak: KPS skor je vrijedan prediktor kliničkog uspjeha kod pacijenata koji se podvrgavaju pleurodezi talkom zbog MPE.

Ključne riječi: Karnofsky skala, VATS, talk pleurodeza, maligni pleuralni izljev

INTRODUCTION

Malignant pleural effusion (MPE) is a common complication of various cancers, including lung, breast, and ovarian malignancies, often indicating advanced disease and poor prognosis (1). It results from the accumulation of malignant cells within the pleural space, leading to debilitating symptoms such as dyspnoea, cough, and chest pain. The management of MPE aims to alleviate these symptoms and improve overall quality of life, with pleurodesis being a cornerstone of palliative treatment.

Video-assisted thoracoscopic surgery (VATS) talc pleurodesis is a widely accepted procedure for managing MPE. It involves the instillation of sterile talc into the pleural space during thoracoscopy, promoting adhesion of the pleura and preventing recurrent effusions (2). Numerous long-term studies have demonstrated that VATS talc pleurodesis is effective in controlling MPE, with success rates ranging from 68% to 85% (3,4). The procedure is associated with significant improvements in symptoms, particularly dyspnoea, and is generally well-tolerated by a majority of patients.

Diferent factors have been identified that influence the success of pleurodesis - these include the extent of pleural disease, the underlying malignancy, and the patient's overall performance status. The Karnofsky Performance Status (KPS) score is a widely used tool to assess a patient's functional status and ability to perform daily activities. It ranges from 0 (death) to 100 (normal functioning), with higher scores indicating better functional status (5). The cornerstone for assessing the success of pleurodesis is a clinical and radiological presence/absence of pleural effusion within the first three months after the pleurodesis. Therefore, the procedure was considered successful if, even after three months, there were no signs of pleural fluid reaccumulation. Complete success was verified in patients when there was no reaccumulation within three months after the intervention, a partial when a smaller reaccumulation compared to the state before pleurodesis was observed, and the procedure is unsuccessful when there is a so-called status quo before-after the procedure or even greater reaccumulation of fluid inside the pleural cavity.

Various methods of pleurodesis and sclerosing agents are available for use, including talc, doxycycline, and bleomycin. According to updates on British Thoracic Society (BTS) guidelines from 2023, talc is still the most commonly used sclerosing agent due to its effectiveness and safety profile (6).

Techniques for talc instillation include VATS talc poudrage, talc slurry via thoracostomy, indwelling pleural catheters (IPC), and different combination approaches (e.g. initial drainage via IPC followed by talc instillation). VATS talc poudrage boasts success rates exceeding 90%, with non-life-threatening short-term adverse effects such as fever and pain, and is considered the gold standard for pleurodesis in patients with recurrent MPE (7).

AIM

The aim of the study was to evaluate whether the KPS score could reliably predict the clinical success of VATS talc pleurodesis in patients diagnosed with MPE, and to determine which pleurodesis procedure offered the most success during a three-month follow-up.

MATERIAL S AND METHODS

Study design

This retrospective, comparative cohort study was conducted at the Clinic of Thoracic Surgery, Clinical Center University of Sarajevo, a tertiary care center, within a two-year period. The study was designed to evaluate the predictive value of the KPS score in determining the clinical success of three different talc pleurodesis modalities used for the management of MPE.

Study population

A total of 180 patients diagnosed with malignant pleural effusion were included in the study.

Inclusion criteria were:

- Age ≥18 years;
- Radiologically and/or cytologically confirmed MPE;
- Underwent either VATS talc pleurodesis, talc slurry via tube thoracostomy, or placement of an indwelling pleural catheter (IPC);
- Documented Karnofsky Performance Status score at the time of intervention ≥70%;
- Life expectancy over 30 days.

Exclusion criteria included:

- Non-malignant pleural effusions;
- Patients with incomplete follow-up data or missing KPS scores;
- Patients who underwent pleurodesis for pneumothorax or other indications;
- Documented Karnofsky Performance Status score at the time of intervention <70%;
- Life expectancy less than 30 days.
- Atelectasis due to endobronchial obstruction;
- Lung entrapment and trapped lung;
- Pregnancy;
- Previous radiotherapy applied to the surface of the entire hemithorax.

Group allocation

A total of 180 patients diagnosed with MPE were included in the study and divided into one of the following groups:

- Group 1 (VATS Talc Pleurodesis): 60 patients underwent VATS with talc poudrage. Sterile graded talc (4-5 grams) was insufflated into the pleural space under direct thoracoscopic visualization following complete drainage of pleural fluid and confirmation of full lung expansion. A chest tube (typically 20-32 Fr) was placed postoperatively and managed until drainage reduced to <100 mL/day.
- Group 2 (Talc Slurry via Tube Thoracostomy): 60 patients received talc slurry pleurodesis. After chest tube insertion and adequate drainage, 4-5 grams of sterile talc suspended in 100 mL of normal saline was instilled through the tube. The tube was clamped for 1 hour, then unclamped and connected to an underwater seal. Tube removal criteria were similar to Group 1.
- Group 3 (IPC): 60 patients underwent placement of an IPC. Patients or caregivers were instructed on intermittent drainage (3-4 times per week) until spontaneous pleurodesis or clinical decision to cease use. Talc instillation via IPC was not performed in this group.

Karnofsky Performance Status (KPS) Assessment

The KPS score was assessed by a trained clinician at the time of admission and before the intervention. Scores ranged from 0 to 100 in 10-point increments, with higher scores indicating better functional status.

Data Collection

Demographic data (age, sex), type of intervention, KPS score, length of hospital stay, and follow-up imaging were retrieved from electronic medical records and procedural logs. Chest radiographs or CT scans were reviewed to assess for recurrence.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. The chi-square test was used for categorical variables, and ANOVA was used for continuous variables to compare across the three groups. Logistic regression analysis was performed to determine the independent predictive value of KPS on pleurodesis success. A p-value <0.05 was considered statistically significant. Statistical analysis was conducted using SPSS Statistics v19.

RESULTS

Among 180 patients included in this study, 73 (40%) were male, and 107 (60%) were female patients (male to female ratio 1:1.47). The average age was 63.97±8.75 years. The subjects were divided into four age groups (55-59, 60-64, 65-69, and 70-74 years of age - the youngest patient being 31 and the oldest 80).

The average length of hospital stay was 7.22±1.37 days (from 5 to 13 days), and according to predefined groups as follows: G1-6.68±1.16 days, (from 5 to 12 days), G2-7.44±1.40 days (from 6 to 13 days) and G3-7.52±1.41 days (from 7 to 13 days) (Figure 1).

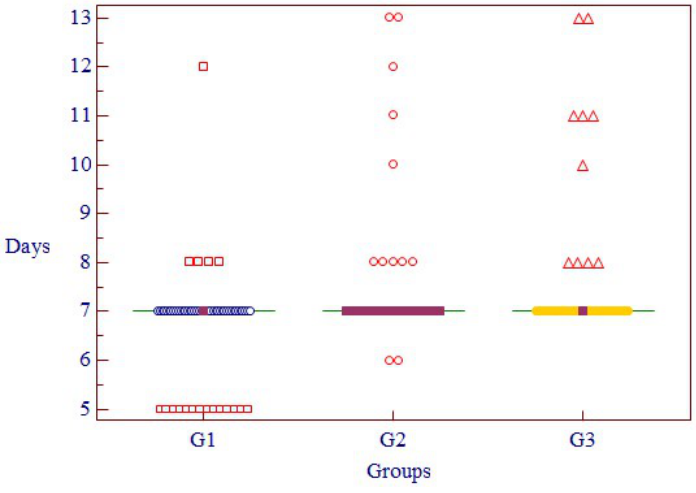

Figure 1 **Average hospital stay (days) by predefined patient groups.**

The outcome of talc pleurodesis by predefined groups (G1, G2 and G3) after three months is demonstrated in Table 1.

Table 1 **The outcome of talc pleurodesis among three groups of patients after three months.**

The outcome	G1	G2	G3
Complete success	91% (55/60)	64% (38/60	48% (29/60)
Partial success	7% (4/60)	32% (20/60)	48% (29/60)
Unsuccessful	2% 1/60)	4 (2/60)	4% (2/60)
Total	100% (60/60)	100% (60/60)	100% (60/60)

Test of significance	G1vsG2	G2vsG3	G1vsG3
Chi-squared	14.994	2.481	27.32
Degrees of Freedom (DF)	2	2	2
Significance level	P = 0.0006	P = 0.2893	P < 0.0001
Contingency coefficient	0.332	0.142	0.431

The calculated x2 test showed a statistically significant difference in pleurodesis success after the third month between groups G1 and G2 ($x2=14.994$, $p = 0.0006$) and G1 and G3 ($x2=27.32$, $p<0.0001$). Yate's Continuity Correction (Yates's chi-squared test) was applied.

KPS score before and after pleurodesis, as well as inferential statistics for KPS Paired samples t-test for each group of patients before and after pleurodesis was calculated. Using the Student's t-test for dependent samples, a statistically significant difference was found in the value of the KP score before and after pleurodesis in group G1 before the intervention ($M=74.83$, $SD=8.92$) and after the intervention ($M=94.33$, $SD=8.71$), $t = 25.41$, $p<0.0001$ (Table 2).

Table 2 **Inferential statistics for Karnofsky Paired samples t-test for group G1 before and after pleurodesis.**

	G1	
KPS score	Before pleurodesis	After pleurodesis
Sample size	60	60
Arithmetic mean	74.8333	94.3333
95% CI for the mean	72.5281 to 77.1386	92.0840 to 96.5827
Variance	79.6328	75.8192
Standard deviation	8.9237	8.7074
Standard error of the mean	1.1520	1.1241

Paired samples t-test

Mean difference	19.5000
Standard deviation	5.9447
95% CI	17.9643 to 21.0357
Test statistic t	25.409
Degrees of Freedom (DF)	59
Two-tailed probability	P < 0.0001

Using the Student's t-test for dependent samples, a statistically significant difference (t = 16.94, p<0.0001) was determined in the value of the KPS score before and after pleurodesis among patients in group G2, as shown in Table 3.

Table 3 **Inferential statistics for Karnofsky Paired samples t-test for group G2 before and after pleurodesis**

	G2	
KPS score	Before pleurodesis	After pleurodesis
Sample size	60	60
Arithmetic mean	70.9836	85.5738
95% CI for the mean	68.7555 to 73.2117	83.1656 to 87.9820
Variance	75.6831	88.4153
Standard deviation	8.6996	9.4029
Standard error of the mean	1.1139	1.2039

Paired samples t-test

Mean difference	14.5902
Standarddeviation	6.7265
95% CI	12.8674to 16.3129
Test statistict	16.941
Degreesof Freedom(DF)	59
Two-tailed probability	P < 0.0001

Using the Student's t-test for dependent samples, a statistically significant difference (t = 18.05, p<0.0001) was determined in the value of the KPS score before and after pleurodesis in group G3 (Table 4).

Table 4 **Inferential statistics for Karnofsky Paired samples t-test for group G3 before and after pleurodesis.**

	G3	
KPS score	Before pleurodesis	After pleurodesis
Sample size	60	60
Arithmetic mean	68.0000	82.5000
95% CI for the mean	65.5378 to 70.4622	79.6612 to 85.3388
Variance	90.8475	120.7627
Standard deviation	9.5314	10.9892
Standard error of the mean	1.2305	1.4187

Paired samples t-test

Mean difference	14.5000
Standarddeviation	6.2232
95% CI	12.8924to 16.1076
Test statistict	18.048
Degreesof Freedom(DF)	59
Two-tailed probability	P < 0.0001

Moreover, using the Student's t-test for dependent samples, a statistically significant difference (t = -5.315, p<0.0001) was determined in the value of the KPS score after performing pleurodesis between groups G1 and G2 (Table 5), as well as between groups G1 and G3 (t = -6.537, p<0.0001) (Table 6). On the other hand, no statistically significant difference (t = -1.654, p<0.1007) was found in the KPS score after pleurodesis between groups G2 and G3.

Table 5 **Comparison of KPS score after pleurodesis between G1 and G2 groups.**

	KPS score after pleurodesis	
	G1_2	G2_2
Sample size	60	60
Arithmetic mean	94.3333	85.5738
95% CI for the mean	92.0840 to 96.5827	83.1656 to 87.9820
Variance	75.8192	88.4153
Standard deviation	8.7074	9.4029
Standard error of the mean	1.1241	1.2039
F-test for equal variances	P = 0.556	

T-test (assuming equal variances)

Difference	-8.7596
PooledStandardDeviation	9.0648
StandardError	1.6482
95% CI of difference	-12.0232 to-5.4960
Test statistict	-5.315
Degreesof Freedom(DF)	118
Two-tailedprobability	P < 0.0001

Table 6 **Comparison of KPS score after pleurodesis between G1 and G3 groups.**

	KPS score after pleurodesis	
	G1_2	G3_2
Sample size	60	60
Arithmetic mean	94.3333	82.5000
95% CI for the mean	92.0840 to 96.5827	79.6612 to 85.3388
Variance	75.8192	120.7627
Standard deviation	8.7074	10.9892
Standard error of the mean	1.1241	1.4187
F-test for equal variances	P = 0.076	

T-test (assuming equal variances)

Difference	-11.8333
Pooled Standard Deviation	9.9142
Standard Error	1.8101
95% CI of difference	-15.4178 to-8.2489
Test statistic t	-6.537
Degrees of Freedom (DF)	118
Two-tailed probability	P < 0.0001

DISCUSSION

VATS talc pleurodesis is widely regarded as the most effective intervention for MPE. Among 180 patients enrolled in this retrospective, comparative cohort study, VATS talc pleurodesis was performed in 60 patients. The findings of our study align with studies indicating high success rates for VATS talc pleurodesis, particularly in patients with good performance status. For instance, a systematic review of thirty-four studies involving 4626 patients reported significant improvements in dyspnea and performance status post-VATS pleurodesis (8). Moreover, a systematic review highlighted that VATS talc pleurodesis is associated with improved survival and quality of life in MPE patients (9). According to the aforementioned study by Basso SM, et al., there was a statistically significant difference (p=0.014) in the value of the KPS score, which was 62.1±12.2 before, and 71.3±13.2 after VATS talc pleurodesis.

Our study underscores the critical role of performance status in predicting the success of pleurodesis procedures. Patients with higher KPS scores tend to have better outcomes post-VATS talc pleurodesis. This finding is consistent with previous research, which has shown that performance status is a significant predictor of survival and pleurodesis success in MPE patients (10).

Several studies have demonstrated that talc slurry pleurodesis via tube thoracostomy can be successful in patients with MPE, though success rates may vary depending on patient selection and technique. IPCs offer a less invasive option, allowing for outpatient management; however, their efficacy in achieving long-term pleurodesis is variable, and they are generally considered a palliative measure rather than a definitive treatment (11). In our study, a complete success (no fluid reaccumulation) within three months of the procedure was observed in 55 (91%) of patients in G1, 38 (64%) of patients in group G2, and 29 (48%) of patients in G3. An article in Shanghai Chest discussed a study by Rena et al., which involved 172 patients undergoing VATS talc poudrage. By three months, 49% of patients had a complete response with no re-accumulation of pleural effusion, and the majority maintained this response at 12 months. This underscores the efficacy of VATS talc pleurodesis in achieving sustained pleurodesis within the first three months (12).

While our study provides valuable insights, it is not without limitations. The retrospective design and potential selection bias inherent in such studies may affect the generalizability of our findings. Future prospective, multicenter studies are warranted to validate our results and explore the role of other factors, such as pleural fluid analysis and tumor biology, in predicting pleurodesis outcomes.

CONCLUSION

The KPS score is a valuable predictor of clinical success in patients undergoing talc pleurodesis for MPE. Moreover, VATS talc pleurodesis is more effective in achieving long-term pleurodesis and disease-free interval in comparison to other means of talc pleurodesis in the treatment of MPE.

REFERENCES

1. Beltsios ET, Mavrovounis G, Adamou A, Panagiotopoulos N. Talc pleurodesis in malignant pleural effusion: a systematic review and meta-analysis. Gen Thorac Cardiovasc Surg. 2021;69(5):832-42. doi: 10.1007/s11748-020-01549-2.
2. Brega-Massone PP, Lequaglie C, Magnani B, Ferro F, Cataldo I. Chemical pleurodesis to improve patients' quality of life in the management of malignant pleural effusions: the 15 year experience of the National Cancer Institute of Milan. Surg Laparosc Endosc Percutan Tech. 2004;14(2):73-9. doi: 10.1097/00129689-200404000-00005.
3. Xia H, Wang XJ, Zhou Q, Shi HZ, Tong ZH. Efficacy and safety of talc pleurodesis for malignant pleural effusion: a meta-analysis. PLoS One. 2014;9(1):e87060. doi: 10.1371/journal.pone.0087060.
4. Cardillo G, Facciolo F, Carbone L, Regal M, Corzani F, Ricci A, et al. Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions. Eur J Cardiothorac Surg. 2002;21(2):302-5; discussion 305-6. doi: 10.1016/s1010-7940(01)01130-7.
5. Leemans J, Dooms C, Ninane V, Yserbyt J. Success rate of medical thoracoscopy and talc pleurodesis in malignant pleurisy: A single-centre experience. Respirology. 2018;23(6):613-7. doi: 10.1111/resp.13252.
6. Subedi A, Banjade P, Joshi S, Sharma M, Surani S. Updates on British Thoracic Society Statement on Pleural Disease and Procedures 2023. Open Respir Med J. 2023;17:e18743064286775. doi: 10.2174/0118743064286775231128104253.
7. Gayen S. Malignant pleural effusion: Presentation, diagnosis, and management. Am J Med. 2022;135(10):1188-92. doi:10.1016/j.amjmed.2022.04.017
8. Hassan M, Gadallah M, Mercer RM, Harriss E, Rahman NM. Predictors of outcome of pleurodesis in patients with malignant pleural effusion: a systematic review and meta-analysis. Expert Rev Respir Med. 2020;14(6):645-54. doi: 10.1080/17476348.2020.1746647.
9. Basso SM, Mazza F, Marzano B, Santeufemia DA, Chiara GB, Lumachi F. Improved quality of life in patients with malignant pleural effusion following videoassisted thoracoscopic talc pleurodesis. Preliminary results. Anticancer Res. 2012;32(11):5131-4. PMID: 23155293.
10. Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. Chest. 2000;117(1):73-8. doi: 10.1378/chest.117.1.73.
11. Lee YCG, Light RW. Management of malignant pleural effusions. Respirology. 2004;9(2):148-56. doi.org/10.1111/j.1440-1843.2004.00566.x.
12. Ali JM, Aresu G, Peryt A, Coonar AS. Video-assisted thoracoscopic surgery in the management of mesothelioma. Shanghai Chest. 2018;2:46. doi:10.21037/shc.2018.05.05.

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Epidemiological Analysis of Acute Poisonings in Children and Adolescents

Epidemiološka analiza akutnih trovanja kod djece i adolescenata

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ABSTRACT

Introduction: acute poisonings represent a significant public health issue in the pediatric population, with patterns varying according to age and intent. Aim: to determine the number and characteristics of children and adolescents diagnosed with acute poisoning who were examined and/or hospitalized at a tertiary level hospital during a one-year period. Materials and methods: a retrospective analysis was conducted for children and adolescents up to 18 years of age who were examined at the Emergency Department of the Pediatric Clinic, Clinical Center University of Sarajevo, for acute poisoning in the period between 1 January and 31 December 2023. Demographic data, type of toxin, intent of poisoning, and need for hospitalization were analyzed. Data were processed using descriptive statistics. Results: out of total of 10.500 examinations, acute poisoning was confirmed in 87 patients (0.83%). Accidental poisonings accounted for 65.5%, and intentional in 34.5% cases. Accidental poisonings were predominant in the 0.6-5 years group, whereas intentional were most frequently observed among adolescents (15-18 years), particularly girls. The most common cause were drugs (56.3%). A total of 29 patients (33.3%) were admitted for hospital treatment, including 6 to the intensive care unit, and 11 patients at psychiatry. The study results were compared with a previous research period within the same institution (2010-2013). Conclusion: an increase in acute poisonings was observed, particularly intentional poisonings in adolescence, indicating a deterioration in youth mental health. Targeted preventive strategies are needed, including parental education, monitoring of adolescents' emotional well-being, and strengthening cooperation between pediatric and psychiatric services.

Keywords: acute poisoning, children, adolescents, prevention

SAŽETAK

Uvod: akutna trovanja predstavljaju značajan javnozdravstveni problem u pedijatrijskoj populaciji, s obrascima koji variraju prema dobi i namjeri. Cilj: utvrditi broj i karakteristike djece i adolescenata s dijagnozom akutnog trovanja pregledanih i/ili hospitaliziranih na tercijarnom nivou zdravstvene zaštite tokom jednogodišnjeg perioda. Materijali i metode: provedena je retrospektivna analiza medicinske dokumentacije djece i adolescenata do 18 godina koja su u periodu od 1. januara do 31. decembra 2023. godine pregledana u Prijemnoj ambulanti Pedijatrijske klinike Kliničkog centra Univerziteta u Sarajevu, zbog akutnog trovanja. Analizirani su demografski podaci, vrsta toksina, namjera trovanja i potreba za hospitalizacijom. Podaci su obrađeni deskriptivnom statistikom. Rezultati: od ukupno 10.500 pregleda, akutna trovanja potvrđena su kod 87 pacijenata (0,83%). Slučajna trovanja činila su 65,5%, a namjerna 34,5% slučajeva. Slučajna trovanja bila su dominantna u dobi 0,6–5 godina, a namjerna među adolescentima (15-18 godina), naročito djevojkama. Najčešći uzrok trovanja su lijekovi (56,3%). Ukupno 29 pacijenata (33,3%) primljeno je na hospitalni tretman, od čega 6 u jedinicu intenzivne njege, a 11 pacijenata upućeno na psihijatriju. Rezultati istraživanja komparirani su sa rezultatima prethodnog istraživačkog perioda u okviru iste ustanove (2010-2013). Zaključak: uočen je porast broja akutnih trovanja, posebno namjernih u adolescentskoj dobi, što ukazuje na pogoršanje mentalnog zdravlja mladih. Potrebne su ciljane preventivne strategije koje uključuju edukaciju roditelja, praćenje emocionalnog stanja adolescenata, te jačanje saradnje između pedijatrijskih i psihijatrijskih službi.

Ključne riječi: akutna trovanja, djeca, adolescenti, prevencija

INTRODUCTION

Acute poisonings represent a significant public health problem in the pediatric population, encompassing a wide range of causative agents, clinical manifestations, and outcomes (1,2,3). Among individuals under 18 years of age, the causes and patterns of poisoning largely depend on the child's developmental stage. The highest number of cases is recorded between the ages of one and five years, when children, driven by curiosity and a lack of awareness of danger, often come into contact with potentially toxic substances in the household environment (3). In this age group, unintentional poisonings predominate, most commonly involving medications, cleaning agents, and other household chemicals (4). With increasing age, the pattern of poisoning changes. In later childhood, and especially during adolescence, intentional poisonings become more frequent, often associated with emotional disorders, consequent tendency towards self-harm, experimentation with psychoactive substances, or alcohol. The clinical presentation of acute poisoning can be nonspecific, and the severity of symptoms varies depending on the type of substance, dose, route of exposure, and timeliness of medical intervention (5). Poisoning cases most often require a multidisciplinary approach, which includes not only emergency medical care but also psychological or psychiatric assessment and support when necessary (5,6). Education and increased awareness among parents and caregivers, as well as the implementation of safety measures in the home environment, are integral components of strategies aimed at reducing the incidence of acute poisonings in this vulnerable population (7,8).

Although acute poisonings are a common reason for pediatric emergency visits, available data remain limited. Epidemiological studies are recommended to enable a better understanding of local patterns and to support the development of effective preventive strategies (9).

AIM

The aim of this study was to determine the number of children and adolescents under 18 years of age diagnosed with acute poisoning examined and/or hospitalized at the tertiary healthcare level during a one-year period, and to analyze the characteristics of poisonings with respect to age, gender, type of toxic substance, and intent of exposure (unintentional or intentional). An additional aim was to determine the number of children who required hospitalization at the Pediatric Clinic of the CCUS for stabilization and detoxification.

MATERIALS AND METHODS

This study was a retrospective analysis based on a review of medical records, including outpatient protocols and medical histories of children and adolescents under 18 years of age who presented to the Emergency Department of the Pediatric Clinic of the CCUS in the period from 1 January to 31 December 2023. Data were collected from the hospital archive and included basic demographic information (age, gender), the type of ingested toxic substance, the manner of poisoning (unintentional or intentional), as well as the number of patients requiring hospitalization. The analysis included cases in which the diagnosis of poisoning was confirmed and documented in the medical records. The collected data were processed using descriptive statistics, and the results were presented in tabulations.

RESULTS

In the period from 1 January to 31 December 2023, a total of 10,500 patients were examined at the Admission Outpatient Clinic of the Pediatric Clinic of the CCUS.

Acute intoxications were confirmed in 87 patients (0.83%), of which 65.5% were accidental and 34.5% intentional. Accidental intoxications most frequent occured in the age group of 0.6 months to 5 years, while intentional poisonings were most prevalent among adolescents aged 15-18 years, particularly among girls (Table 1).

Table 1 **Distribution of intoxications in children and adolescents by age, gender, and type of poisoning (intentional or accidental).**

Age Group	Gender	Intentional N (%)	Accidental N (%)	Total N (%)
0.6-5 years	m	0	17	17
	f	0	18	18
Total		0 (0.0)	35 (40.2)	35 (40.2)
6-10 years	m	1	3	4
	f	1	4	5
Total		2 (2.3)	7 (8.0)	9 (10.3)
11-14 years	m	2	4	6
	f	3	4	7
Total		5(5.7)	8 (9.2)	13 (14.9)
15-18 years	m	8	2	10
	f	15	5	20
Total		23 (26.4)	7 (8.0)	30 (34.5)
All age groups	m	11	26	37
	f	19	31	50
Total		30 (34.5)	57 (65.5)	87 (100)

The most common cause of poisoning was medications (n = 49; 56.3%), with 22 cases being intentional and 27 accidental. Accidental medication poisonings were predominantly recorded in children aged 1-5 years (n = 16), whereas the majority of intentional medication poisonings were observed among adolescents aged 15-18 years (n = 19), accounting for 86% of all intentional medication poisonings. Poisonings with non-corrosive substances (detergents, cleaning products) were reported in 16 cases, nearly all (n = 15) accidental, most frequently among children aged 0.6 months to 5 years (n = 13). Poisonings with corrosive substances were documented in seven cases, four of which were intentional, occurring mainly in older age groups (6-18 years). Alcohol poisonings were observed only in older children and adolescents (11-18 years), with a total of six cases, two of which were intentional. Poisonings with rodenticides, plants, and carbon monoxide were rare, mostly accidental, and occurred mainly in younger children (Table 2).

Table 2 **Types of intoxications in children and adolescents by age, intent, and type of substance.**

Type of Substance	Intent	Age Group				Total N=87
		0.6-5 years	6-10 years	11-14 years	15-18 years	
Medications	Intentional	0	1	2	19	22
	Accidental	16	5	5	1	27
Non-corrosive substances	Intentional	0	0	0	1	1
	Accidental	13	1	1	0	15
Corrosive substances	Intentional	0	1	2	1	4
	Accidental	3	0	0	0	3
Alcohol	Intentional	0	0	0	2	2
	Accidental	0	0	1	3	4
Rodenticides	Intentional	0	0	0	0	0
	Accidental	0	1	0	0	1
Plants	Intentional	0	0	0	0	0
	Accidental	3	0	1	0	4
Carbon monoxide CO	Intentional	0	0	0	0	0
	Accidental	0	0	4	0	4
Total		35	9	16	27	87

Hospitalization in a standard ward was recorded in 23 cases (26.4%), most frequently among adolescents (15-18 years; n = 10) and children aged 11-14 years (n = 5). Admission to the Pediatric Intensive Care Unit was required for a total of six patients (6.9%), distributed across all age groups, indicating a smaller number of severe clinical conditions. Eleven patients required referral to psychiatric services, almost exclusively adolescents (15-18 years) (Table 3).

Table 3 **Management of children and adolescents with intoxication by age group.**

Age Group	Hospitalized – Standard Ward	Observation and Referral to Psychiatry	Pediatric Intensive Care Unit	Returned to Home Care	Total
0.6–5 years	5	0	2	26	35
6–10 years	3	2	0	4	9
11–14 years	5	0	2	9	16
15–18 years	10	11	2	4	27
Total	23	15	6	43	87

DISCUSSION

Analysis of data collected in the period from 1 January to 31 December 2023, at the Pediatric Clinic of the CCUS revealed a total of 87 cases of acute poisoning, representing 0.83% of the 10,500 patients examined during the said period. This frequency significantly exceeds previously reported rates of acute poisoning in the same institution, where a total of 80 cases were recorded over three years (2010-2013), ranging from 0.42% to 0.67% per year (10). In a single year, the number of intoxications exceeds the cumulative number from the previous three-year series, clearly indicating an increase in this health problem among children and adolescents.

Consistent with the presented results, age and gender distribution of poisonings among children and adolescents could be observed. Accidental poisonings were most frequently recorded in the youngest age group (0.6-5 years), which was expected given the developmental characteristics of this population, their pronounced curiosity, lack of awareness of dangers, and easy access to toxic substances in the home environment. These findings are in agreement with other studies, which also confirm a higher incidence of unintentional intoxications in early childhood (11,12). These data highlight the importance of increased parental vigilance and the implementation of preventive measures, particularly education on the safe storage of medications and chemicals, as well as continuous supervision of young children as key preventive strategies. Additionally, reduced supervision, easily accessible toxic substances, elevated parental stress, and certain behavioral patterns increase the risk of poisoning among children. Lack of adequate supervision has been recognized as a key risk factor, emphasizing the importance of close parental presence. Caregiver education should stress the importance of supervision and safe storage of hazardous substances adapted for children, particularly between the ages of 1 and 3 (13).

On the other hand, the rise in intentional poisonings among adolescents (15-18 years of age), particularly among girls, is concerning, as it may indicate the presence of emotional difficulties, impulsive behavior, or self-harming attempts. These results align with global trends reporting an increasing prevalence of mental health problems in adolescence, including depression, anxiety, and suicidal behavior (14). Gender differences, with girls beeing more frequently involved in intentional intoxications, further emphasize the need for a gender-sensitive approach in prevention, early identification, and intervention among adolescents. Such an approach should involve schools, families, and healthcare services, with focus on mental health and access to psychological support.

Particular concern arises from the distribution of poisonings by age and intent. While in the earlier period, poisonings were mostly accidental and predominant among children aged 1-5 years, an increase in intentional poisonings was recorded in 2023. A total of 30 intentional poisonings were documented, representing 34.5% of all intoxications, the majority of which occurred in adolescents. This is in complete contrast to previous results from the same institution, in which no cases of poisoning were reported among children older than 14 years. Medications remain the most common cause of poisoning, consistent with earlier data (10).

Even more concerning was the fact that 11 patients (12.6%) who were intentionally poisoned were referred to the Psychiatry Clinic immediately after a short observation period, while 29 patients (33.3%) were admitted for inpatient treatment, six of whom required Pediatric Intensive Care for stabilization and detoxification before psychiatric assessment. This finding indicates the severity of the clinical picture and the complexity of managing these patients, who require urgent and integrated medical-psychiatric intervention.

Overall, the data indicate the need for different prevention strategies tailored to age and the specific needs of children and adolescents, ranging from physical protection and parental education in early childhood to systematic support and monitoring of emotional status and behavior in adolescents (13,15).

CONCLUSION

The findings of this study demonstrate a significant and concerning increase in acute poisonings among children and adolescents, both in absolute numbers and relative to overall pediatric visits. Of particular concern was an increase in intentional poisonings, which were almost absent in earlier years and now predominantly affect adolescents over 14 years of age, reflecting a deterioration in youth mental health and underscoring the need for a comprehensive, systemic response from healthcare and educational systems. Effective prevention requires strengthening educational efforts for parents, schools, and the broader community to raise awareness about poisoning risks, safe storage of hazardous substances, emotional support, and early recognition of psychological distress. Additionally, clear and structured collaboration between pediatric services, child and adolescent psychiatry, mental health centers, and social services is essential to ensure rapid and coordinated management of cases. Continuous epidemiological monitoring and analysis of poisoning trends are necessary to detect shifts in behavioral patterns and guide targeted preventive measures. Prioritizing the mental health of children and adolescents in public health policy, through comprehensive prevention programs, improved access to psychological support, and stigma reduction, is crucial. Ultimately, the rise in intentional poisonings among adolescents signals not only a medical challenge but also broader social and emotional issues, requiring an integrated, multi-sectoral approach to protect and support young people.

REFERENCES

1. AlGhadeer HA, Alturaifi RY, AlGhafli JA, Alshawker MH, AlBisher AM, AlGhadeer FA, et al. Patterns and Outcomes of Acute Poisoning Among Children Presenting to Emergency Department in AlAhsa, Saudi Arabia. Cureus. 2024;16(12):e76565. doi: 10.7759/cureus.76565.
2. Sayed HY, Elawady R, Elyamany MI, Hemeda MS. Assessment of acute poisoning in children using poisoning severity scores: A cross-sectional study at Damietta General Hospital Egypt. Toxicol Rep. 2024;13:101735. doi: 10.1016/j.toxrep.2024.101735.
3. Singer CE,Văru□ RM, Singer M, Cosoveanu S, Razzak AJ, Popescu ME, et al. Epidemiological and Clinical Characteristics of Pediatric Acute Drug Intoxications: A Retrospective Analysis. Children (Basel). 2024;12(1):44. doi: 10.3390/children12010044.
4. Alanazi MQ, Al-Jeraisy M, Salam M. Severity scores and their associated factors among orally poisoned toddlers: a cross sectional single poison center study. BMC Pharmacol Toxicol. 2016;17:1. doi: 10.1186/s40360-015-0044-7.
5. Corlade-Andrei M, Nedelea PL, Ionescu TD, Rosu TS, Hauta A, Grigorasi GR, et al. Pediatric Emergency Department Management in Acute Poisoning-A 2-Year Retrospective Study. J Pers Med. 2023;13(1):106. doi: 10.3390/jpm13010106.
6. Schwebel DC, Evans D, Hoeffler SE, Marlenga BL, Nguyen SP, Jovanov E, et al. Unintentional child poisoning risk: A review of causal factors and prevention studies. Children's Health Care. 2016;46(2):109-3030. doi.org/10.1080/02739615.2015.1124775
7. Romeeh E, Abd El Sattar Ahmed M, Ibrahim WKK. Mothers' awareness about poisoning prevention among their children under five years old. Egypt J Health Care. 2022;13(4):725-43. doi: 10.21608/ejhc.2022.265087
8. Wynn PM, Zou K, Young B, Majsak-Newman G, Hawkins A, Kay B, et al. Prevention of childhood poisoning in the home: overview of systematic reviews and a systematic review of primary studies. Int J Inj Contr Saf Promot. 2016;23(1):3-28. doi: 10.1080/17457300.2015.1032978.
9. Nguyen SN,Vu LT, Nguyen HT, Nguyen LMT. Childhood Acute Poisoning at Haiphong Children's Hospital: A 10-Year Retrospective Study. Int J Pediatr. 2023;2023:2130755. doi: 10.1155/2023/2130755.
10. Slatina E, Avdanović A. Characteristics of acute poisoning in children. Timočki Medicinski Glasnik. 2015;40(1):9-19 ref. 7.
11. Zhang H, Huo Q, Jing R, Dong M. Clinical analysis of acute poisoning in children. BMC Pediatr. 2024;24(1):212. doi: 10.1186/s12887-024-04697-z.
12. Wojciechowki J, Czapla M, Konop M, Juárez-Vela R, Rosińczuk J. Evaluation of Accidental and Intentional Pediatric Poisonings: Retrospective Analysis of Emergency Medical Service Interventions in Wroclaw. Polish Nursing Reports. 2024;14(3):2523-34. doi.org/10.3390/nursrep14030186.
13. Schmertmann M, Williamson A, Black D, Wilson L. Risk factors for unintentional poisoning in children aged 1-3 years in NSW Australia: a case-control study. BMC Pediatr. 2013;13:88. doi: 10.1186/1471-2431-13-88.
14. Hawton K, Saunders KE, O'Connor RC. Self-harm and suicide in adolescents. Lancet. 2012;379(9834):2373-82. doi: 10.1016/S0140-6736(12)60322-5.
15. Ding Y, Xiang J, Hu Y, Wu L, Lu Z, Ye M. Adolescent Self-Poisoning Decision-Making Behavior: A Qualitative Study Using the Theory of Planned Behavior. J Psychosoc Nurs Ment Health Serv. 2025;63(8):43-51. doi: 10.3928/02793695-20250320-03.

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The Incidence of Colorectal Cancer in Two Time Periods at the Clinic for General and Abdominal Surgery of the Clinical Center of the University of Sarajevo

Učestalost pojave kolorektalnog karcinoma u dva vremenska perioda na Klinici za opću i abdominalnu hirurgiju Kliničkog centra Univerziteta u Sarajevu

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ABSTRACT

Introduction: colon cancer is the most common cancer of the digestive tract. It is also known as colorectal cancer depending on its location. As a rule, cancer arises on the mucosa, and if it is unrecognized, it continues to spread into the deeper layers of the intestine, sometimes even breaking through the entire wall of the intestine. In 2020, it is estimated that there were more than 1.9 million newly diagnosed patients and that of this number, there were about 930,000 deaths. There is also a big difference in the geographical diversity of the occurrence of colon cancer, so that the incidence rate was the highest in Europe, New Zealand and Australia, and the highest mortality rate was precisely in Europe. Aim: to compare patients who were surgically treated at our Clinic in two time periods, in 2019 and 2023 respectivelly, compared to operated patients published in other studies. Materials and methods: materials used in the research were patients, of whom 93 were surgically treated in 2019 and 130 in 2023, which was a total of 223 patients. They were processed in seven variables, specifically the average number of years of the patient, the gender of the patient, localization, whether it was a curative or palliative operation, the presence of metastases and the need for a stoma. The methods used in the research were Fisher's test, Mann-Whitney test and X2 test. Results: the results of the research showed a statistically significant difference only in the number of operations between the two years and in the number of open stomas, since the calculation showed that patients operated on in 2023 had a 3.72 times higher chance of getting a stoma. No statistically significant difference was found in the other processed variables, which at the same time represents the conclusion of the study with the recommendation that the next study should be done over a longer period of time and on a larger number of patients.

Keywords: colorectal cancer, localization, sex, age, curative surgery

SAŽETAK

Uvod: karcinom debelog crijeva predstavlja najčešći karcinom probavnog trakta. Poznat je još i kao kolorektalni karcinom ovisno o svojoj lokalizaciji. U pravilu karcinom nastaje na mukozi te ukoliko je neprepoznat nastavlja svoje širenja u dublje slojeve crijeva ponekada čak i sa probojem cijele stijenke crijeva. U 2020 godini procjena je da je bilo više od 1.9 miliona oboljelih novootkrivenih pacijenata te da je od tog broja bilo oko 930000 smrtnih ishoda. Velika je i razlika i u geografskoj različitosti pojave karcinoma debelog crijeva tako da je stopa incidencije bila najviša u Europi, Novom Zelandu i Australiji, a najviša stopa smrtnosti je bila upravo u Europi. Cilj: komparacija pacijenata koji su operirani na našoj klinici u dva vremnska perioda i to u 2019 i 2023 godini u odnosu na operirane pacijente objavljene u drugim studijama. Materijali i metode: materijali korišteni u istraživanju su pacijenti od kojih je 2019 godine operisano 93 a 2023 godine 130 što je ukupan broj od 223 pacijenta. Obrađeni su u sedam varijabli i to su prosječan broj godina oboljelih, spol pacijenta, lokalizacija, da li se radilo o kurativnoj ili palijativnoj operaciji, prisutnost metastaza i potrebe za izvođenjem stome. Metode korištene u istraživanju su Fisherov test, Mann-Whitney test i X2 test. Rezultati: rezultati dobiveni istraživanjem pokazuju statistički značajnu razliku samo u broju operacija između naveden dvije godine i u broju otvorenih stoma budući da je izračunom dobiveno da su pacijenti operisani u 2023 imali 3.72 puta veću šansu za dobivanje stome. U ostalim obrađenim varijablama nije pronađena statistički značajna razlika što ujedno predstavlja zaključak studije uz preporuku da bi se sljedeća studija trebala uraditi u većem vremenskom razmaku na većem broju pacijenata.

Ključne riječi: kolorektalni karcinom, lokalizacija, spol, dob, kurativna hirurgija

INTRODUCTION

Mortality from colon cancer is decreasing in more advanced and developed countries precisely because of the timely detection of tumors with the help of screening of patients who have predisposing factors, i.e. active screening of healthy patients who do not have any symptoms but are old enough to expect the appearance of precancerous lesions. which can subsequently lead to cancer if they are not removed in time (1,2).

The incidence of cancer depends on its location, so that about half of colon tumors arise in the rectum and sigmoid colon, up to 20% in the cecum and ascending colon, while the incidence in the transverse and descending colon is about 15% each. The appearance of carcinoma of the cecum as well as of the ascending colon mostly has a polypoid appearance, but an increase in macroscopically different ulcer-type forms that may or may not bleed has been observed. Rarely, this localization causes any problems, and their symptoms are revealed only in the advanced stage of the disease (3).

Carcinomas of the colon located more distally than the ascendens are mostly ring-shaped and can involve the entire circumference of the colon and, due to their mass, can cause subocclusive disorders (4).

Histologically, the most common type of colon cancer is adenocarcinoma, which can be classified into two stages of differentiation.Well-differentiated carcinomas that are characterized by glands lined with highly cylindrical epithelium that are most often seen in adenomas that represent precancerous lesions but are not carcinomas.

Weakly differentiated carcinomas are made up of strands of cells or clusters of cells and they cause a strong desmoplastic reaction of the organism, which is why they have a firmer consistency on palpation.

Mucinous colorectal adenocarcinomas belong to a special subtype of cancer, producing large amounts of mucus that separates the intestinal wall and this mucus moves the nucleus of the cells, giving the appearance of a signet ring, and these cancers are extremely malignant, aggressive, that is, cancers with a very poor prognosis (5,6,7,8).

According to the mechanism and method of spread, colorectal cancer spreads in several ways.The first way is through the intestinal wall itself and through lymphovascular or perineural infiltration.Also, by passing through the peritoneum itself, it can spread with the same causes of peritoneal carcinomatosis. They can metastasize to the liver via the portal vein, while carcinomas of the distal part of the colon most often metastasize to the lungs via the inferior vena cava (9,10).

It is precisely the stage of expansion of the tumor that gives us a picture of the prognosis of the outcome of surgical treatment, which can be curative and palliative. Classification of tumor extension is divided into two classifications. The so-called TNM calcification and DUKES classification.

Statistically speaking, survival within 5 years for Dukes I is 90%, for Dukes B 70%, Dukes C 35-65% and for Dukes D survival drops to only 4%.

Another classification is TNM calcification where T represents tumor, N represents lymph nodes and M distant metastases.

AIM

The aim of this study was to conduct a comparative analysis of colorectal cancer and its basic characteristics in a period of one year with a distance of four years between the examined years (i.e. the research was carried out in 2019 and 2023). These two years were chosen because the COVID virus pandemic was declared during that period, and it was assumed that patients would not report to their doctor on time due to fear and the reduced number of surgical procedures, and the overall increased number of patients in 2019 compared to 2013 was considered the reason for the increase in the number of patients and subsequent opening of stomas in terms of palliative surgical procedures.

MATERIALS AND METHODS

This study was part of a retrospective analysis that included 223 patients treated at the Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo in un the period from 2019 to 2023. In 2019, 93 patients were surgicaly treated and 130 patients in 2023.

The methods of statistical analysis that were used were Fisher's test, Mann-Whitney test, X2 test.

RESULTS

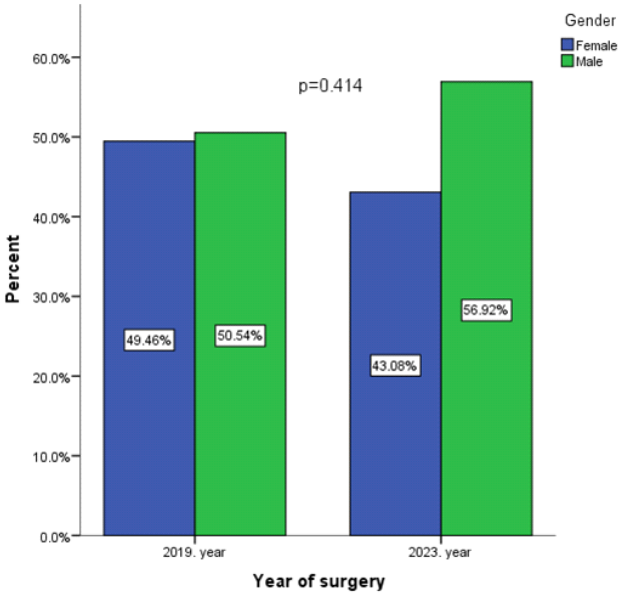

Figure 1 **Distribution of gender by year of surgery.**

In 2019, a total of 93 patients were surgically treated, of which 46 (49.5%) were women, and 47 (50.5%) were men. In 2023, a total of 130 patients were surgically treated, of which 56 (43.1%) were women and 74 (56.9%) were men. The results of the Fisher test did not indicate a statistically significant difference in the gender distribution between 2019 and 2023 ($p = 0.414$), (Figure 1).

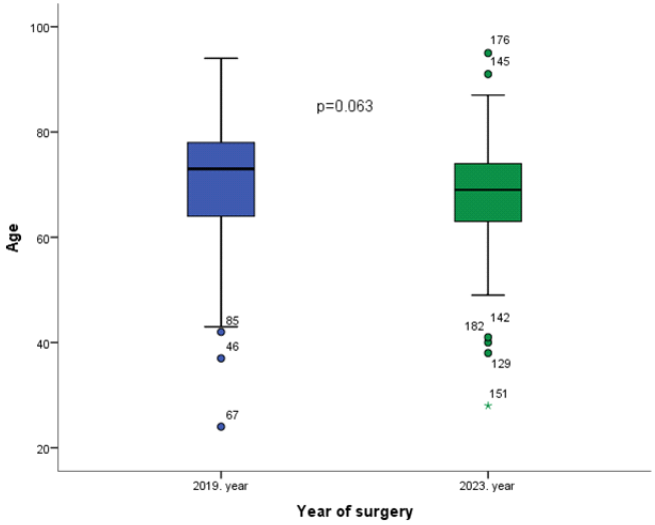

Figure 2 **Distribution of age by year of surgery.**

The median age of patients surgically treated in 2019 was 70.88 years (IQR = 15). The youngest patient was 24, while the oldest patient was 94. The median age of patients surgically treated in 2023 was 69.00 years (IQR = 11). The youngest patient was 28, while the oldest patient was 95. The Mann-Whitney test found no statistically significant difference in the age of the patients in relation to the year of surgery (p=0.063), (Figure 2).

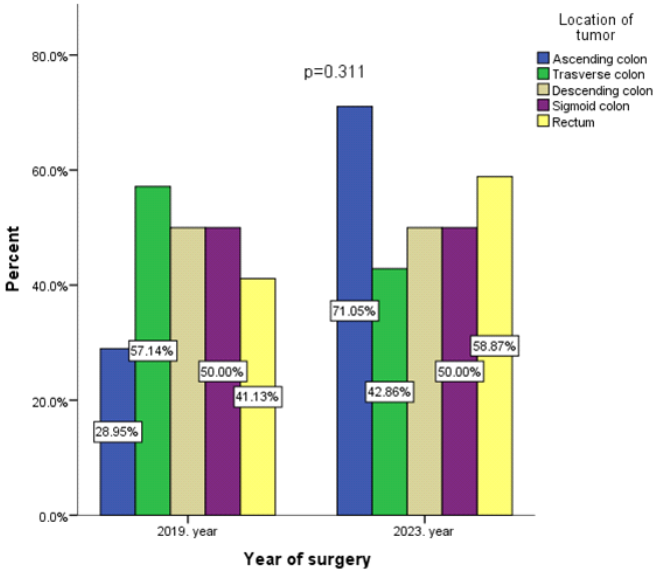

Figure 3 **Distribution of tumor locations by year of surgery.**

In 2019, 11 (28.9%) patients had a tumor on the ascending colon, while in 2023, that percentage was 27 (71.1%). In 2019, 4 (57.1%) patients had a tumor at the transverse colon, while 3 (42.9%) patients had a tumor at that location in 2023. On the descending column, 5 (50%) patients had a tumor in 2019, while in 2023 the same number of 5 patients (50%) was recorded. In 2019, 22 (50%) patients had a tumor in the sigmoid colon, and in 2023, also 22 (50%) patients had a tumor in that location. Finally, 51 (41.1%) patients had a rectal tumor in 2019, while in 2023 that number increased to 73 (58.9%). The X2 test did not find a statistically significant difference in the distribution of tumor locations based on the year of operation (p=0.311), (Figure 3).

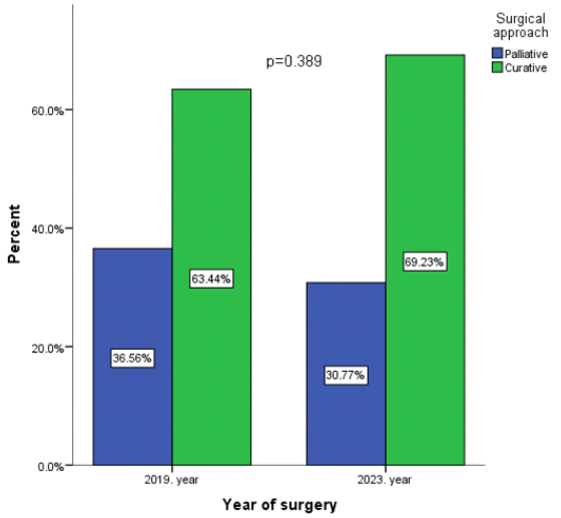

Figure 4 **Distribution of surgical approaches by year of surgery.**

In 2019, 34 (36.6%) patients underwent palliative surgery, while 59 (63.4%) patients underwent curative surgery. In 2023, 40 (30.8%) patients had palliative surgery, while 90 (69.2%) underwent curative surgery. Fisher's test did not find a statistically significant difference in the type of surgery in relation to the year of surgery (p = 0.389), (Figure 4).

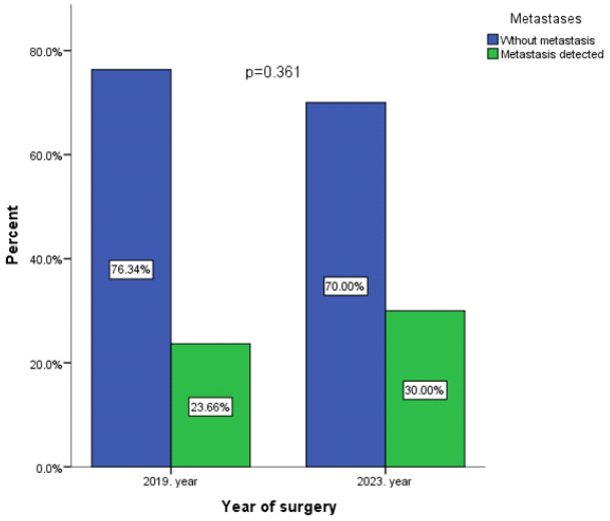

Figure 5 **Distribution of metastatic disease by year of surgery.**

In 2019, 71 (76.3%) patients did not have metastatic disease, while 22 (23.7%) patients had metastatic disease. In 2023, 91 (70%) patients did not have metastatic disease, while 39 (30%) patients had metastatic disease. Fisher's test did not find a statistically significant difference in the presence of metastatic disease in relation to the year of operative treatment (p = 0.361), (Figure 5).

Figure 6 **Distribution of stoma creation by year of surgery.**

In 2019, 80 (86.0%) patients did not have a stoma, while 13 (14.0%) patients had a stoma. In 2023, 81 (62.3%) patients did not have a stoma, while 49 (37.7%) patients had a stoma. Fisher's test determined a statistically significant difference in stoma performance between patients operated on in 2019 and 2023 ($p<0.001$). Additionally, analysis found that patients operated on in 2023 were 3.72 times more likely to have a stoma compared to patients operated on in 2019 ($p=0.011$), (Figure 6).

DISCUSSION

The results of this study did not show a significant statistical difference in the gender of the treated patients. In 2019, there were a total of 93 operated patients, of which 46 were women (49.5 %), and 47 were men (50.5 %). In 2023, a total of 130 patients were surgically treated, of which 56 were women (43.1%) and 74 were men (56.9%). Comparing our results with the results published in the scientific paper by Wang H, et al. we concluded that their study comprised 37.6% women and 62.4% men, which did not represent a statistically significant difference .

The average age of patients who were surgically treated in 2019 was 70.88 years. The youngest patient was 24 and the oldest was 94. The median age in 2023 was 69.00 years, and the youngest patient was 28 and the oldest was 95. No statistically significant difference was found in this variable in relation to the year of surgery. Comparing the results with the study not mentioned above, it was reported that the largest number of patients with CRC were in the age range of 61-70, 53.5%, 24% of patients were older than 70, 19% from 51-60, and 40-50 year 3.5%. The published results did not show a statistically significant difference compared to our work from 2019 and 2023.

According to tumor localization, in 2019, 11 patients (28.9%) had cancer in the ascending colon, while in 2023, that number was 27 (71.1%). Infiltration of the transverse colon was present in 4 patients (57.1%) in 2019, while in 2023 that number was 3 (42.9%). On the descending colon, 5 (50%) patients had cancer in 2019, which is the same number in 2023. In 2019, 22 (50%) had sigmoid colon cancer, the same as in 2023, 22 patients (50%). In the end, 51 (41.1%) patients had rectal cancer in 2019, while that number of patients increased to 73 (58.9%) in 2023. The X2 test did not find a statistically significant difference according to tumor localization.

Comparing the results from the above study, information is obtained that in their study the colon is divided into 3 parts, namely the proximal colon, which includes the cecum, ascendens and up to the transversum, the distal colon, which includes the last part of the transversum, the lien flexure, the descending colon and the sigmoid colon, and to the rectum. The percentage of patients who had cancer in the proximal part of the colon was 17.8%, in the distal part of the colon the percentage of patients was 30.7%, and in the rectal part that percentage was 16.2%. The last part of the percentage goes to the complete colon and precancerous lesions. No statistically significant difference was found in the results.

In the difference between palliative and curative surgery in 2019, 34 patients (36.6%) underwent palliative surgery, while 59 (63.4%) underwent curative surgery. In 2023, 40 patients (30.8%) underwent palliative surgery, while 90 underwent curative surgery. No statistically significant difference between 2019 and 2023 was found in this variable either.

In the study of Zhao X-D, et al. (11), 38.7% of patients underwent palliative surgery while 62.3% underwent curative surgery. A comparison of the results from China and our results did not prove a statistically significant difference. The total number of days of patient hospitalization was 10.

In 2019, 71 patients did not have metastatic disease (76.3%), while 22 did (23.7). In 2023, 91 patients (70%) did not have metastatic disease, while 39 (30%) did. Fisher's test did not find a statistically significant difference in the presence of metastatic disease. The scientific paper by Na H, et al., stated that over 50% of patients would develop metastatic disease (12,13). Treatment of patients with metastatic colon cancer can prolong life by up to 20 months with a multidisciplinary approach with resection of liver metastases with adequate chemo and radio therapy as well as immunotherapy (14,15). Comparing the results of the research, a statistically significant difference was observed in metastatic disease CRCa.

In patients who underwent curative surgery in 2019, there was no relapse of the disease, although some died of natural causes. The absence of relapse is evidence of a radical approach to surgical treatment as well as adequate preoperative oncological preparation of the patient and postoperative oncological treatment.

In the variable of the presence of a stoma in 2019, 80 patients (86.0%) did not have a stoma, while 13 (14%) did. In 2023, 81 patients (62.3%) did not have a stoma, while 49 (37.7%) had a stoma. In this variable, a statistically significant difference was demonstrated in the performance of stoma in patients who were operated on in 2019 compared to 2023, and that patients operated in 2023 were 3.72 times more likely to have a stoma compared to patients from 2019. The percentage of patients who had a stoma opened in China was 40.1%, while there were 59.9% who did not have a stoma opened, which does not represent a statistically significant difference compared to the Clinical Center of the University of Sarajevo.

The number of operated patients in 2019 was 93 and in 2023 it was 130, with a difference of 37 more patients in 2023 compared to 2019.

This type of study needs to be done over a longer period of time and with a larger number of patients. We recommend a two-year period with a longer time distance.

CONCLUSION

With this study, which included 7 variables (number of operated, sex, age, localization, curative or palliative surgery, metastases and stoma), a statistically significant difference was proven in only two variables, namely the incidence of stoma and the number of operated patients. Other variables did not show a significant statistical difference. The incidence of performing a stoma is not a feature of palliative treatment, but can also be the importance of a curative operation, since the low localization of rectal cancer requires the operation of rectal amputation, which ends with a terminal stoma. Patient gender did not show a significant statistical difference in the occurrence of metastatic disease. This study did not include tumor staging, but it was proven that the smaller tumor staging (Dukes classification, TNM classification) the bigger cure possibility.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. doi: 10.3322/caac.21660
2. Midgley R, Kerr D. Colorectal cancer. The Lancet. 1999;353(9150):391-9. doi: 10.1016/S0140-6736(98)07127-X.
3. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med. 1990;113(10):779-88. doi: 10.7326/0003-4819-113-10-779. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med. 1990;113(10):779–788. doi: 10.7326/0003-4819-113-10-779.
4. Bettington M, Walker N, Rahman T, Vandeleur A, Whitehall V, Leggett B, et al. High prevalence of sessile serrated adenomas in contemporary outpatient colonoscopy practice. Intern. Med. J. 2017;47:318-23. doi: 10.1111/imj.13329
5. Štulhofer M. Kirurgija probavnog sustava, Zagreb, Medicinska naklada Zagreb;1999
6. Harisson Manual of Medicine, 20th edition, McGraw Hill / Medical; 2019.
7. Donadon M, Ribero D, Morris-Stiff G, Abdalla E K, Vauthey J N. New paradigm in the management of liver-only metastases from colorectal cancer. Gastrointest Cancer Res. 2007;1(01):20-7. PMCID: PMC2632517.
8. Geoghegan JG, Scheele J. Treatment of colorectal liver metastases. Br J Surg. 1999;86(02):158-69. doi: 10.1046/j.1365-2168.1999.01013.x.
9. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol. 2021;14(10):101174. doi: 10.1016/j.tranon.2021.101174
10. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer. 2018;18(01):78. doi: 10.1186/s12885-017-3925-x.
11. Zhao X-D, Cai B-B, Cao R-S, Shi R-H. Palliative treatment for incurable malignant colorectal obstructions: A meta-analysis. World J Gastroenterol. 2013 Sep 7;19(33):5565-74. doi: 10.3748/wjg.v19.i33.5565.
12. Na H, Liu X, Li X, Zhang X, Wang Y, Zhaohui Wang Z, et al. Novel roles of DC-SIGNR in colon cancer cell adhesion, migration, invasion, and liver metastasis. J Hematol Onco. 2017;10(1):28. doi: 10.1186/s13045-016-0383-x.
13. Bhardwaj R, Parker MC. Palliative therapy of colorectal carcinoma: stent or surgery. Colorectal Dis. 2003;5:518-21. doi: 10.1046/j.1463-1318.2003.00519.x
14. Wong RW, Rappaport WD, Witzke DB, Putnam CW, Hunter GC. Factors influencing the safety of colostomy closure in the elderly. J Surg Res. 1994;57:289-92. doi: 10.1006/jsre.1994.114720.
15. Ptok H, Marusch F, Steinert R, Meyer L, Lippert H, Gastinger I. Incurable stenosing colorectal carcinoma: endoscopic stent implantation or palliative surgery. World J Surg. 2006;30:1481-7. doi: 10.1007/s00268-005-0513-z. th Serv. 2025;63(8):43-51. doi: 10.3928/02793695-20250320-03.

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Clinical Characteristics of Patients Undergoing Endovascular Therapy: A Single-Center Experience from Bosnia and Herzegovina

Kliničke karakteristike pacijenata koji se podvrgavaju endovaskularnoj terapiji: iskustvo jednocentrične studije iz Bosne i Hercegovine

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ABSTRACT

Introduction: systemic atherosclerotic conditions, including peripheral artery disease (PAD) and carotid artery disease (CAD), are strongly influenced by hypertension, diabetes mellitus (DM) and smoking. Despite the widespread use of endovascular therapy, data on its use in Southeast European populations remain scarce. Aim: to analyze the clinical characteristics of patients undergoing endovascular procedures. Materials and methods: this retrospective study included 135 patients (65 ± 9 years; 65.2% male) who underwent endovascular intervention at the Clinical Centre University of Sarajevo during 2024. Demographic, clinical, and procedural data were analyzed. Results: technical success was achieved in 86.7% of procedures. Hypertension (86.7%) and DM (51.1%) were the most common comorbidities, while 73.4% of patients were ever-smokers. Current smokers were significantly younger than non-smokers ($p < 0.001$). DM was associated with infragenicular ($p = 0.011$), whereas smoking correlated with aortoiliac lower-extremity lesions ($p = 0.002$). Lipid-lowering therapy was not prescribed before stenting in 9.6% of patients; among those treated, 62% received high- and 38% moderate-intensity statins. Conclusion: in this real-world cohort, DM clustered with distal and smoking with proximal PAD distribution, the latter reflecting accelerated and earlier atherosclerotic disease among smokers. Although statin use was common, pre-procedural underuse and suboptimal dosing indicate a gap in secondary prevention. Prospective multicenter studies are warranted to validate these findings and clarify long-term outcomes.

Keywords: peripheral arterial disease, endovascular procedures, diabetes mellitus, smoking, Bosnia and Herzegovina

SAŽETAK

Uvod: sistemska aterosklerotska stanja, uključujući perifernu arterijsku bolest i karotidnu arterijsku bolest, su pod snažnim uticajem hipertenzije, dijabetesa melitusa i pušenja. Uprkos širokoj primjeni endovaskularne terapije, podaci o njenoj upotrebi u populacijama jugoistočne Evrope i dalje su ograničeni. Cilj: analizirati kliničke karakteristika pacijenata koji se podvrgavaju endovaskularnim procedurama. Materijali i metode: ova retrospektivna studija obuhvatila je 135 pacijenata (prosječna starost 65 ± 9 godina; 65,2% muškaraca) koji su tokom 2024. godine podvrgnuti endovaskularnoj intervenciji na Kliničkom centru Univerziteta u Sarajevu. Analizirani su demografski, klinički i proceduralni podaci. Rezultati: tehnički uspjeh postignut je u 86,7% procedura. Hipertenzija (86,7%) i dijabetes melitus (51,1%) bili su najčešći komorbiditeti, dok su 73,4% pacijenta bili trenutno ili bivši pivši. Trenutni pušači bili su značajno mlađi od nepušača ($p < 0,001$). Dijabetes je bio povezan s infragenikularnim lezijama ($p = 0,011$), dok je pušenje bilo u korelaciji s aortoilijačnim lezijama donjih ekstremiteta ($p = 0,002$). Hipolipemici nisu bili propisani prije postavljanja stenta kod 9,6% pacijenata; među onima koji su je primali, 62% je koristilo statine visokog intenziteta, a 38% umjerenog intenziteta. Zaključak: u ovoj stvarnoj kohorti, dijabetes je bio povezan s distalnim, a pušenje s proksimalnim rasporedom PAB-a, pri čemu potonji odražava ubrzanu i raniju aterosklerotsku bolest kod pušača. Iako je primjena statina bila česta, njihova nedovoljna upotreba prije zahvata i suboptimalno doziranje ukazuju na nedostatke u sekundarnoj prevenciji. Potrebne su prospektivne multicentrične studije kako bi se ovi nalazi potvrdili i razjasnili dugoročni ishodi.

Ključne riječi: periferna arterijska bolest, endovaskularne procedure, dijabetes mellitus, pušenje, Bosna i Hercegovina

INTRODUCTION

Clinical manifestations of systemic atherosclerosis, such as peripheral artery disease (PAD) and carotid artery disease (CAD), frequently coexist, and its prevalence continues to rise due to aging populations and increasing rates of diabetes mellitus (DM), hypertension, dyslipidemia and smoking (1-3).

Endovascular therapy has become the first-line approach for many patients with these diseases, offering a less invasive alternative to surgery with comparable short-term outcomes (4–6). The development of drug-coated stents and advanced imaging guidance has improved procedural success and safety (7). Nevertheless, outcomes remain influenced by patient-specific risk factors and comorbidities (8,9). Diabetes mellitus is particularly associated with distal, infrapopliteal arterial disease and chronic limb-threatening ischemia (CLTI), resulting in poorer long-term patency and limb salvage rates (5,10). In contrast, smoking is more frequently linked to proximal disease and higher rates of restenosis (11). Despite these associations, data on the relationship between risk-factor clustering and anatomic distribution of lesions among patients undergoing endovascular interventions remain limited, especially in Southeast European populations.

AIM

The aim of the study was to analyze the clinical characteristics of patients undergoing endovascular procedures at a tertiary center in Bosnia and Herzegovina, with a specific focus on the association between major cardiovascular risk factors and the anatomic distribution of atherosclerotic disease.

MATERIALS AND METHODS

Study design and setting

This was a retrospective observational, single-center study, conducted at the Clinic of Heart Diseases, Blood Vessels and Rheumatism - Angiology Department of the Clinical Center University of Sarajevo (CCUS). The study included all patients hospitalized in the period between 1 January and 31 December 2024, who underwent endovascular intervention with or without stent implantation. A total of 135 patients were included in the analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data sources and variables

Data were collected from electronic medical records and angiography reports. The following variables were analyzed:

- Demographics: age and sex.
- Comorbidities and risk factors: smoking status, DM, arterial hypertension, previous myocardial infarction, ischemic stroke, thrombophilia, and malignancy.
- Lipid-lowering therapy: type and intensity (high vs moderate).
- In-hospital mortality.
- Anatomical classification of vascular segments: aortoiliac segment (abdominal aorta, common iliac, and external iliac arteries), femoropopliteal segment (common femoral, superficial femoral, and popliteal arteries), infragenicular (below-knee) segment (anterior tibial, posterior tibial, and peroneal arteries), renal artery, supra-aortic arteries (subclavian and vertebral arteries). Common carotid artery (CCA) and internal carotid artery (ICA) were analyzed separately.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as number (percentage). The distribution of continuous variables was assessed for normality using the Kolmogorov–Smirnov test. Age differences between groups were analyzed using independent samples t-test or one-way ANOVA, depending on the number of categories. Levene's test was applied to assess equality of variances; if violated, Welch's correction was used. Associations between categorical variables were assessed using Pearson's χ^2 test with Yates' continuity correction for 2×2 tables and Fisher's exact test when expected cell counts were <5. Monte Carlo estimation was applied only when exact computation was not possible. Statistical significance was defined as $p < 0.05$. All analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 135 patients were included in the study, with a mean age of 65 ± 9 years (ranging from 38 to 90 years). There were 88 men (65.2%) and 47 women (34.8%). Plain old balloon angioplasty (POBA) was reported in 3 (2.2%) patients. One patient underwent stenting of the inferior vena cava (IVC), while all remaining interventions were arterial.

Regarding vascular segments involved, 26 (19.3%) patients had disease of the aortoiliac segment, 53 (39.3%) of the femoropopliteal segment, 25 (18.5%) of the infragenicular arteries, and 15 (11.1%) of the supra-aortic arteries. CCA involvement was present in 54 (40%), ICA in 31 (23%), and renal artery in 3 (2.2%) patients. The affected side was left in 67 (49.6%), right in 50 (37%), and bilateral in 13 (9.6%) patients. The procedure was technically successful in 117 (86.7%) patients. One patient died during hospitalization due to reasons unrelated to the procedure.

Comorbidities were common: hypertension was present in 117 (86.7%), DM in 69 (51.1%), previous myocardial infarction in 24 (17.8%), and ischemic stroke in 6 (4.4%) patients. Thrombophilia was recorded in 2 (1.5%), and malignancy in 3 (2.2%) patients. With respect to smoking status, 78 (57.8%) were current smokers, 21 (15.6%) were former smokers, and 35 (25.9%) were non-smokers. Lipid-lowering therapy was not prescribed previous to stenting in 13 (9.6%) patients. Among those treated, rosuvastatin was the most commonly used statin (72; 53.3%), followed by atorvastatin (47; 34.8 %). 75 (62%) patients were on high-intensity, and 46 (38%) on moderate-intensity statin regimens.

A statistically significant difference in mean age was observed between patients with and without aortoiliac disease ($p < 0.001$), with those having aortoiliac involvement being younger. Patients with hypertension were significantly older compared to those without hypertension ($p = 0.002$). A significant difference in age was noted according to smoking status ($p < 0.001$), with current smokers being the youngest group, and non-smokers the oldest. No other categorical variables showed statistically significant differences in mean age (Table 1).

Table 1 **Comparison of patient age with clinical characteristics.**

Variable	Category	Mean ± SD	p-value
Gender	Female (n=47)	63.57 ± 10.58	0.307
	Male (n=88)	65.38 ± 7.77	
Aortoiliac segment	No (n=109)	66.04 ± 8.44	<0.001*
	Yes (n=26)	59.35 ± 8.67	
Femoropopliteal segment	No (n=82)	64.87 ± 9.33	0.848
	Yes (n=53)	64.57 ± 8.14	
Infragenicular segment	No (n=110)	64.09 ± 8.86	0.070
	Yes (n=25)	67.64 ± 8.40	
Supra-aortic arteries	No (n=120)	64.94 ± 8.58	0.475
	Yes (n=15)	63.20 ± 11.05	
Internal carotid artery	No (n=104)	64.11 ± 9.44	0.056
	Yes (n=31)	66.90 ± 6.17	
Common carotid artery	No (n=77)	63.82 ± 9.57	0.228
	Yes (n=54)	65.72 ± 7.74	
Affected side	Right (n=50)	65.04 ± 7.57	0.140
	Left (n=67)	65.03 ± 9.13	
	Bilateral (n=13)	60.08 ± 8.35	
Smoking status	No (n=35)	69.49 ± 8.70	<0.001*
	Yes (n=78)	61.92 ± 7.93	
	Ex-smoker (n=21)	67.52 ± 8.68	
Diabetes mellitus	No (n=66)	63.35 ± 9.43	0.072
	Yes (n=69)	66.09 ± 8.10	
Hypertension	No (n=17)	58.47 ± 10.64	0.002*
	Yes (n=117)	65.61 ± 8.25	
Previous myocardial infarction	No (n=109)	64.11 ± 9.30	0.100
	Yes (n=24)	67.42 ± 6.26	
Lipid-lowering therapy	No (n=13)	65.92 ± 7.22	0.588
	Yes (n=121)	64.52 ± 8.99	
Statin dose	Moderate (n=75)	64.51 ± 9.66	0.983
	High (n=46)	64.54 ± 7.89	

Data were presented as mean ± standard deviation (SD) with 95% confidence intervals (CI). Group comparisons were performed using independent-samples t-test for dichotomous variables and one-way ANOVA for variables with more than two categories. Where Levene's test indicated heterogeneity of variances ($p < 0.05$), Welch's t-test was applied. *Statistical significance was set at $p < 0.05$.

A significant association was observed between gender and history of myocardial infarction ($X^2 = 9.35$, $p = 0.002$). Myocardial infarction was more frequent in male patients (25.6%) compared to female patients (4.3%). No statistically significant association with gender was found for any of the other categorical variables.

A significant association was observed between lesion laterality and smoking status ($p = 0.021$). Smoking was more common among patients with bilateral (69.2%) and left-sided (65.7%) lesions, compared to those with right-sided involvement (46.9%). Lesion laterality was not significantly associated with DM, hypertension, previous myocardial infarction, or procedural success.

Table 2 shows association of major cardiovascular risk factors with vascular segments and procedural success. Significant associations were observed for DM and smoking. Patients with diabetes more frequently had infragenicular ($p = 0.011$) and lower extremity involvement in general ($p = 0.041$), while ICA disease was significantly less common among them ($p = 0.003$). Ever-smokers (current or former smokers) had significantly higher prevalence of aortoiliac ($p = 0.002$) and lower extremity lesions ($p = 0.009$) compared to non-smokers. No statistically significant associations were found between hypertension or previous myocardial infarction and any vascular segment or procedural success (Table 2).

Table 2 **Association of major cardiovascular risk factors with vascular segments and procedural success.**

Variable	DM Yes/no (%)	P	HTA Yes/no (%)	P	Smoking Ever/never (%)	P	Previous MI Yes/no (%)	P
Aortoiliac segment	17.4 / 21.2	0.731	18.8 / 23.5	0.743	26.3 / 0.0	0.002*	12.5/ 20.2	0.565
Femoropopliteal segment	46.4 / 31.8	0.120	39.3 / 35.3	0.959	44.4/ 25.7	0.081	54.2/ 36.7	0.176
Infragenicular segment	27.5 / 9.1	0.011*	17.9 / 23.5	0.523	16.2 / 25.7	0.320	8.3/ 21.1	0.246
Lower extremities	78.3 / 60.6	0.041*	68.4 / 76.5	0.693	76.8 / 51.4	0.009*	62.5/ 70.6	0.591
Supra-aortic arteries	11.6 / 10.6	1.000	11.1 / 11.8	1.000	11.1 / 11.4	1.000	4.2/ 11.9	0.464
Internal carotid artery	11.6 / 34.8	0.003*	24.8 / 11.8	0.358	18.2 / 34.3	0.084	33.3/ 21.1	0.309
Common carotid artery	33.3 / 50.0	0.079	42.6 / 31.3	0.553	37.5 / 50.0	0.284	56.5/ 38.3	0.169
Procedural success	86.4 / 90.9	0.583	87.7 / 94.1	0.691	90.3 / 88.1	0.681	91.3/ 88.8	1.000

DM- Diabetes Mellitus; HTA- Hypertension, MI- Myocardial Infarction. Data are presented as percentages of patients with and without the specified risk factor (yes/no). Associations were analyzed using Pearson's X^2 test or Fisher's exact test where appropriate. *Statistical significance was defined as $p < 0.05$.

DISCUSSION

In this single-center retrospective cohort of 135 consecutive patients undergoing endovascular procedures, we observed a high overall technical success and clear risk factor–specific anatomic patterns: diabetes mellitus (DM) clustered with infragenicular, while smoking history clustered with aortoiliac disease. A total of 73.4% of patients reported a history of smoking, with current smokers being the youngest group, supporting evidence that tobacco exposure accelerates the onset of atherosclerosis and symptomatic PAD, underscoring its role as a major modifiable risk factor (11).

Most interventions were PTA ± stenting or carotid artery stenting (CAS), with a minority being POBA only. High technical success with low in-hospital mortality supports the safety of contemporary endovascular practice in routine care. Our success rate (~87%) aligns with contemporary series reporting 85-95%, depending on lesion complexity and technique (8,9).

Comorbidities were frequent, reflecting the systemic nature of atherosclerosis. Hypertension and DM were most common, emphasizing the metabolic component (3,12). A history of myocardial infarction or stroke, though less common, highlights the systemic character of atherosclerosis (1,2). Low rates of thrombophilia and malignancy suggest that traditional cardiovascular risk factors remain dominant in this population (1,2).

Our anatomic clustering mirrors established evidence: DM is linked to distal PAD and CLTI through medial calcification and microvascular dysfunction, complicating revascularization and long-term patency (10,13). Smoking-related PAD, including proximal aortoiliac involvement, is well documented and biologically plausible given smoking's pro-inflammatory and endothelial effects (11,14).

Interestingly, ICA disease appeared less frequent among patients with DM, contrasting with population-based and surgical series reporting higher or comparable carotid involvement (15,16). Possible explanations include selection bias diabetic patients more often present with advanced lower-extremity disease diverting attention from carotid evaluation as well as small sample size and methodological differences.

Lipid-lowering therapy was absent in 9.6% of patients, a relatively high rate considering guideline recommendations. Among treated individuals, 62% received high-intensity and 38% moderate-intensity statins, suggesting suboptimal implementation of lipid management. Current guidelines recommend high-intensity statin therapy for all PAD patients to achieve ≥50% LDL-C reduction and LDL <1.4 mmol/L (4,17). Suboptimal use may reflect drug intolerance, limited awareness, or therapeutic inertia (18-20). Previous studies show that high-intensity statins improve survival, reduce cardiovascular and limb events, and enhance amputation-free survival (7,15). As only pre-procedural data were available, post-intervention optimization could not be assessed.

The study limitations were as follows: only in-hospital outcomes were analyzed, without long-term follow-up for patency, reintervention, limb salvage, or mortality. The small number of unsuccessful procedures precluded multivariate analysis, and unmeasured confounding (e.g., body mass index, lipid levels, inflammation) cannot be excluded. The single-center design may also limit generalizability.

CONCLUSION

In this real-world cohort, endovascular therapy achieved high technical success. DM clustered with distal and smoking with proximal lower-extremity disease, the latter reflecting accelerated atherosclerotic progression. These findings reinforce risk factor–targeted management-intensive glycemic control, smoking cessation, and routine statin therapy. Large-scale multicenter studies with extended follow-up are warranted to clarify long-term outcomes and procedural success across diverse patient profiles.

REFERENCES

1. Shamaki GR, Markson F, Soji-Ayoade D, Agwuegbo CC, Bamgbose MO, Tamunoinemi BM. Peripheral artery disease: a comprehensive updated review. Curr Probl Cardiol. 2022;47(11):101082. doi: 10.1016/j.cpcardiol.2021.101082.
2. Eid MA, Mehta KS, Goodney PP. Epidemiology of peripheral artery disease. Semin Vasc Surg. 2021;34(1):38-46. doi:10.1053/j.semvascsurg.2021.02.005.
3. Mandaglio-Collados D, Marín F, Rivera-Caravaca JM. Peripheral artery disease: update on etiology, pathophysiology, diagnosis and treatment. Med Clin (Barc). 2023;161(8):344-50. doi: 10.1016/j.medcli.2023.06.005.
4. Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS guideline for the management of lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149(24):e1313-410. doi: 10.1161/CIR.0000000000001251.
5. Daher G, Upadhyay S, Li J. Chronic limb-threatening ischemia: a comprehensive review. Interv Cardiol Clin. 2025;14(2):257-72. doi: 10.1016/j.iccl.2024.11.011.
6. Okoro G, Owunnah FK, Applegate CC, Nelappana MBB, Dobrucki IT, Dobrucki LW. Cutting-edge approaches to diagnosing and treating limb ischemia in peripheral arterial disease. Prog Biomed Eng (Bristol). 2025. doi 10.1088/2516-1091/ae16f1
7. Tanaka R. Recent update on peripheral arterial endovascular therapy for peripheral arterial occlusive disease. Interv Radiol (Higashimatsuyama). 2020;5(3):120-7. doi: 10.22575/interventionalradiology.2020-0014
8. Yoon YH, Lee JH, Hwang WM, Park HW, Roh JH, Lee SJ, et al. Treatment extent of femoropopliteal disease and clinical outcomes following endovascular therapy. EuroIntervention. 2024;20(18):e1154-62. doi: 10.4244/EIJ-D-24-00037.
9. Zilinyi RS, Alsaloum M, Snyder DJ, Raja A, Mintz AJ, Sethi SS, et al. Surgical and endovascular therapies for below-the-knee peripheral arterial disease: a contemporary review. J Soc Cardiovasc Angiogr Interv. 2024;3(3 PtA):101268. doi: 10.1016/j.jscai.2023.101268
10. Thiruvoipati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients with diabetes: epidemiology, mechanisms, and outcomes. World J Diabetes. 2015;6(7):961-9. doi: 10.4239/wjd.v6.i7.961.
11. Wang W, Zhao T, Geng K, Yuan G, Chen Y, Xu Y. Smoking and the pathophysiology of peripheral artery disease. Front Cardiovasc Med. 2021;8:704106. doi: 10.3389/fcvm.2021.704106
12. Mlačo A, Mlačo N, Mekić M, Džubur A. Epidemiology of hospitalized patients with peripheral arterial disease in Bosnia and Herzegovina. Med Glas (Zenica). 2021;18(2):468-74. doi: 10.17392/1397-21.
13. Zhu K, Qian F, Lu Q, Li R, Qiu Z, Li L, et al. Modifiable lifestyle factors, genetic risk, and incident peripheral artery disease among individuals with type 2 diabetes: a prospective study. Diabetes Care. 2024;47(3):435-43. doi: 10.2337/dc23-1503.
14. Ishida M, Sakai C, Kobayashi Y, Ishida T. Cigarette smoking and atherosclerotic cardiovascular disease. J Atheroscler Thromb. 2024;31(3):189-200. doi: 10.5551/jat.RV22015.
15. Zeng Q, Zhang C, Liu X, Yang S, Ma M, Tang J, et al. Prevalence and associated risk factors of carotid plaque and artery stenosis in China: a population-based study. Front Med. 2025;19(1):64-78. doi: 10.1007/s11684-024-1088-0.
16. Liao M, Chen S, Guo R. Association between carotid ultrasonographic parameters and microvascular and macrovascular complications in diabetes: A systematic review and meta-analysis. J Diabetes Complications. 2023;37(8):108554. doi: 10.1016j.jdiacomp.2023.108554.
17. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88. doi: 10.1093/eurheartj/ehz455.
18. Jansen-Chaparro S, López-Carmona MD, Cobos-Palacios L, Sanz-Cánovas J, Bernal-López MR, Gómez-Huelgas R. Statins and peripheral arterial disease: a narrative review. Front Cardiovasc Med. 2021;8:777016. doi: 10.3389/fcvm.2021.777016.
19. Walker M, Riggs KA, Rohatgi A, Beckman J, Addo T, Girotra S, et al. Role of lipids and lipid management therapy among patients with peripheral artery disease: a reappraisal of the current evidence and future directions. J Am Heart Assoc. 2025;14(19):e039734. doi.org/10.1161/JAHA.124.039734.
20. Campia U, Gerhard-Herman M, Piazza G, Goldhaber SZ. Peripheral artery disease: past, present, and future. Am J Med. 2019;132(10):1133-41. doi: 10.1016/j.amjmed.2019.04.043.

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Incidence of Caeserean Section in Pregnancies Following in Vitro Fertilization: A Retrospective Observational Study

Incidenca carskog reza u trudnoćama zanijetim metodom in vitro fertilizacije: retrospektivna opservacijska studija

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ABSTRACT

Introduction: cesarean section is an operative way of completing childbirth, the frequency of which is continuously increasing worldwide. According to the World Health Organization, the optimal cesarean rate at the population level is between 10% and 15%, but in many countries the rates exceed 30%. Assisted Fertilization (AFP) methods, especially in vitro fertilization (IVF), are associated with an increased risk of caesarean section. Aim: to evaluate the incidence of caesarean section in IVF pregnancies and compare it with spontaneously conceived pregnancies and to determine the incidence of caesarean section in pregnancies that conceived through in vitro fertilization (IVF) at private clinics in Bosnia and Herzegovina, and delivered at the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo, in the 2020-2024 period, and to compare it with pregnancies conceived spontaneously. Materials and methods: a retrospective observational study included all births occurred in the Clinical Center University of Sarajevo in the period from 1 January 2020 to 31 December 2024. Pregnant women with IVF conception and a control group with spontaneous conception were analyzed. Variables included maternal age, parity, gestational age, indications for caesarean section, and neonatal outcomes. Statistical analysis included x^2 test, t-test and multivariate logistic regression. $P < 0.05$ was considered significant. Results: a total of 300 IVF pregnancies and 600 spontaneous ones. The incidence of caesarean section in the IVF group was 68%, and in the spontaneous 42% ($p < 0.001$). Independent risks for caesarean section were IVF conception, maternal age >35 years and primiparity. Conclusion: IVF pregnancies have a higher frequency of caesarean section. An individualized approach and education of pregnant women is recommended.

Keywords: caesarean section, IVF, assisted reproduction, maternal outcomes, Bosnia and Herzegovina

SAŽETAK

Uvod: carski rez je operativni način dovršetka porođaja čija učestalost kontinuirano raste širom svijeta. Prema Svjetskoj zdravstvenoj organizaciji, optimalna stopa carskog reza na populacionom nivou je između 10% i 15%, ali u mnogim zemljama stope prelaze 30%. Metode potpomognute oplodnje (MPO), posebno in vitro fertilizacija (IVF), povezane su sa povećanim rizikom od carskog reza. Ova studija ima za cilj da procijeni incidencu carskog reza kod trudnoća nastalih IVF-om i uporedi je sa spontano začetim trudnoćama kao i da utvrdi incidencu carskog reza kod trudnoća koje su začeće ostvarile putem in vitro fertilizacije (IVF) na privatnim klinikama u BiH, a koje su porod obavile na Klinici za ginekologiju i akušerstvo KCUS-a u periodu 2020-2024, i uporediti sa trudnoćama spontano začetim. Materijali i metode: retrospektivna opservacijska studija obuhvata sve porođaje u KCUS-u u periodu od 1. januara 2020. do 31. decembra 2024. Analizirane su trudnice sa IVF začećem i kontrolna grupa sa spontanim začećem. Varijable uključuju starost majke, paritet, gestacijsku starost, indikacije za carski rez i neonatalne ishode. Statistička analiza je obuhvatila x^2 test, t-test i multivarijatnu logističku regresiju. $P < 0,05$ je smatrano značajnim. Rezultati: Ukupno 300 IVF trudnoća i 600 spontanih. Incidenca carskog reza u IVF grupi bila je 68%, a u spontanoj 42% ($p < 0,001$). Nezavisni rizici za carski rez bili su IVF začeće, starost majke >35 godina i primiparitet. Zaključak: trudnoće nastale IVF-om imaju veću učestalost carskog reza. Preporučuje se individualiziran pristup i edukacija trudnica.

Ključne riječi: carski rez, IVF, potpomognuta oplodnja, majčinski ishodi, Bosna i Hercegovina

INTRODUCTION

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. Several different factors in either the male or female reproductive systems can cause infertility. Causes that are related to females are age (> 38 years of age, especially), ovulation disorders, endometriosis, structural anomalies of reproductive organs, autoimmune diseases, environmental toxins, pelvic inflammatory diseases, chromosomal disorders (e.g., Turner syndrome), etc. For males, causes can be different; some of them are chromosomal disorders (e.g., Klinefelter syndrome), genetic disorders (e.g., cystic fibrosis), undescended testicles, previous chemotherapy or radiation therapy, low testosterone (hypogonadism), sexually transmitted diseases, etc. But in more than 20 % of cases, the cause of infertility is unknown (1).

As a treatment option for infertility, assisted reproductive technology (ART) is used. It refers to techniques that manipulate oocytes outside of the body, with in vitro fertilization (IVF) being the most common type. The term "in vitro" means outside a living organism, as oocytes mature in vivo in the ovary and embryos develop into pregnancy in the uterus, but the oocytes are fertilized in a petri dish. In July 1978, Robert Edwards, PhD and Patrick Steptoe, MD, reported the first live birth with IVF in England. This achievement earned Dr. Edwards the Nobel Prize in Medicine in 2010 (2).

IVF plays a crucial role in addressing various infertility issues. Although IVF has helped millions of infertile couples become pregnant, it also carries potential risks for both mothers and infants. These procedures in some cases involve the transfer of more than one embryo, resulting in multiple-gestation pregnancies and deliveries. Multiple births increase the mother's risk of caesarean delivery, maternal hemorrhage, pregnancy-related hypertension, and gestational diabetes. Infant risks include prematurity, low birth weight, mortality, and an increased risk of birth abnormalities and developmental disability. Furthermore, singleton pregnancies conceived via ART may have a higher risk of low birth weight and preterm than singletons conceived without ART (3). Between 1 and 5% of children in industrialized countries are born following assisted reproductive technologies (ART). ART has been associated with higher caesarean section rates compared to women who conceive spontaneously. The overall rate of caesarean sections continues to increase at rapid rate. The ideal caesarean section rate is 10-15% according to the World Health Organization (WHO) (4).

High rates of caesarean deliveries pose a serious public health threat, not only because of the potential maternal and neonatal challenges caused by procedures without clinical justification but also because of long-term complications and increased associated costs. Preconception and prenatal care plans following ART should prioritize reducing the risks that may lead to emergency caesarean sections. Additionally, to reduce elective caesarean sections in pregnancies conceived through ART, effective information translation efforts are required at many levels (organizational, provider, and patient) (5). The question is whether Caesarean section has an impact on pregnancy outcomes treatment with assisted reproductive technology (ART). Several clinical studies have explored this issue and come to different conclusions. Retrospective clinical studies found that the live birth rate (LBR) and clinical pregnancy rate (CPR) in women with previous Caesarean section were lower than those with previous vaginal delivery (6,7). Compared to cycles with previous vaginal delivery, embryo transfer took 30 s longer in cycles with previous Caesarean section. The effect of Caesarean section on IVF outcomes has been investigated by some clinical trials, and a systematic review and meta-analysis on this subject would thus be informative (8). Over the last two decades, the usage of IVF in our region has rapidly increased, and so has the importance of understanding the associated maternal and obstetric outcomes.

In vitro fertilization has become increasingly common in Bosnia and Herzegovina as an effective method of assisted reproduction, offering hope to couples experiencing infertility. Since the birth of the first infant conceived with IVF in Bosnia and Herzegovina in 2007, the use of advanced technologies to overcome infertility has become more prevalent, as has the number of fertility clinics providing ART services and procedures.

Today, IVF procedures are performed daily in Bosnia and Herzegovina, as the number of IVF centers continues to increase. There are eight private IVF centers registered in Bosnia and Herzegovina, five of which are based in the capital city of Sarajevo. According to the data provided by the Federal Institute of Health Insurance and Reinsurance, 0.0% of the total number of IVF cycles financed by the Institute were performed in public health institutions. All procedures are performed in private centers, which puts an additional burden on patients and raises issues of transparency and equality in access to treatment. Despite numerous international studies exploring this topic, there is a lack of region-specific data, particularly in Bosnia and Herzegovina, that evaluates the incidence and contributing factors of caesarean sections in IVF pregnancies. Understanding these patterns is crucial for guiding clinical decision-making, improving maternal care, and setting reasonable expectations for patients undergoing IVF.

AIM

The aim of the study was to evaluate the incidence of caesarean section in IVF pregnancies and compare it with spontaneously conceived pregnancies and to determine the incidence of caesarean section in pregnancies conceived through in vitro fertilization (IVF) at private clinics in Bosnia and Herzegovina, and delivered at the Clinic of Gynecology and Obstetrics of the Clinical Center University of Sarajevo, in the 2020-2024 period, and to compare it with pregnancies conceived spontaneously.

MATERIALS AND METHODS

This retrospective observational study was conducted at the Clinic of Gynecology and Obstetrics of the Clinical Center University of Sarajevo. The study included 300 female patients with confirmed pregnancies achieved through in vitro fertilization (IVF), who delivered at the said institution in the period between 2020 and 2024. Inclusion criteria were: (1) confirmed pregnancy achieved through IVF, (2) delivery at the study institution within the specified period, and (3) availability of complete medical records. Patients with IVF-conceived pregnancies who were conceived by other reproductive methods or had incomplete documentation were excluded.

Clinical and demographic data were extracted from patient medical records and delivery data. The collected variables included mode of delivery (vaginal vs. caesarean section), type of delivery assistance (e.g., vacuum extraction, pharmacological induction), gestational characteristics (singleton or multiple pregnancies), fetal presentation, and indications for surgical delivery. Specific obstetric complications (e.g., uterine inertia, cephalopelvic disproportion, fetal distress) were also recorded. IVF pregnancies were defined as those achieved using assisted reproductive technology involving oocyte retrieval and in vitro fertilization. Caesarean section indications were classified as elective or emergency based on clinical documentation. Fetal presentations such as situs transversus and praesentatio pelvina were confirmed via prenatal ultrasound and intraoperative findings.

Clinical records were reviewed to obtain relevant demographic, obstetric, and perinatal data. Information collected included the mode of delivery (vaginal or caesarean section), presence of single or multiple gestations, fetal presentations, induction or augmentation methods, and specific obstetric indications for surgical delivery. Descriptive statistical methods were used to summarize the data. The primary outcome was the incidence of caesarean section among IVF pregnancies, with secondary outcomes including indications for surgical delivery and frequency of obstetric complications. Categorical variables were presented as frequencies and percentages. Statistical analysis was performed using the x^2 test and multivariate logistic regression.

RESULTS

A total of 900 patients were included in this study. The baseline characteristics of the women in the two groups were shown in Table 1. General characteristics such as age, infertility cause, infertility category, BMI, infertility duration, and type of stimulation protocol were not significantly different among the three groups. There were no statistically significant differences in ovarian response-related factors, such as baseline FSH, mean E2 level on the trigger day, dosage of Gn, duration of Gn stimulation, and number of follicles with a diameter ≥14 mm on the trigger day, indicating that the presence of a previous caesarean section scar with or without a defect did not impact ovarian reserve function or the ovarian response. Statistically significant differences were not observed for embryo development-related factors, such as the number of retrieved oocytes, normal fertilization rate, cleavage rate, number of available embryos, and number of high-quality embryos, among the three groups. These results showed that a previous caesarean section did not affect fertilization or early embryo development.

Table 1 **Baseline characteristics of study participants according to by previous delivery modes**.

Parameter	IVF group (*n* = 300)	spontan group (*n* = 600)	*P*
Age (years)	35.05 ± 4.51	35.11 ± 3.97	0.552
Infertility duration (years)	4.71 ± 3.60	4.14 ± 3.13	0.051
	Infertility cause, n(%)		
Tubal factor	149(49.6)	264(44.0)	0.278
Ovary factor	36(12.0)	85(14.2)	
Male factor	40(13.4)	38(6.3)	
Unexplained	24(8.0)	24(4.0)	
Combined	51(17.0)	189(31.5)	
	Infertility category, n(%)		
Primary	10(3.3%)	52(8.7%)	0.0029
Secondary	290(96.7%)	548(91.3%)	
BMI (kg/m^2)	23.21 ± 2.87	23.50 ± 3.11	0.347
Basal FSH (IU/L)	7.00 ± 2.45	6.81 ± 2.39	0.158
	Stimulation protocol, n(%)		
Md-luteal Lupron	191(63.7)	398(66.3)	0.6289
Antagonist	109(36.3)	202(33.7)	
Total gonadotropins (IU)	2951.35 ± 774.28	2914.25 ± 700.88	0.753
Duration of stimulation (days)	9.23 ± 1.60	9.25 ± 1.60	0.990
E_2 level on the trigger day (pg/mL)	3159.21 ± 1928.37	3104.15 ± 1785.13	0.919
Endometrial thickness on the trigger day (mm)	9.87 ± 1.74	9.72 ± 1.82	0.026
Numbers of follicles with a diameter ≥ 14 mm on the day of trigger	10.80 ± 5.27	11.34 ± 5.38	0.328
Retrieved oocytes (n)	10.10 ± 5.60	10.72 ± 5.56	0.281

Table 2 **Subgroup analysis of women with and without fluid in the cavity.**

Parameter	Non-cavity fluid group (*n* =)	Cavity fluid group (*n* = 25)	Crude OR (95%CI)	Adjusted OR (95%CI)
Live birth	22.4%	20.0%	0.86(0.26 ~ 2.83)	1.06(0.26 ~ 4.34)
Positive hCG test	38.8%	28%	0.61(0.21 ~ 1.74)	0.76(0.20 ~ 2.85)
Clinical pregnancy	32.7%	24%	0.65(0.21 ~ 1.94)	0.96(0.24 ~ 3.77)
Mean implantation rate (mean ± SD)	0.26 ± 0.39	0.22 ± 0.41	0.95(0.79 ~ 1.15)	1.01(0.84 ~ 1.20)
Early abortion	4/16	0/6		
Ectopic pregnancy	0/16	1/6		

(Adjusted for age, infertility cause, infertility category, BMI, endometrial thickness at the hCG trigger, fertilization methods, the number of embryos transferred, high-quality embryos transferred, and day of transfer).

Table 2 presents the results of the subgroup analysis of women who with and without fluid in the cavity (non-cavity fluid group=***cavity fluid group=***). The live birth rate, biochemical pregnancy rate, clinical pregnancy rate, and mean implantation rate in the cavity fluid group were all lower than those in the non-cavity fluid group. However, there were no statistically significant differences in any pregnancy outcome between the two subgroups before and after adjustment for confounders (P>0.05)

Table 3 **Delivery outcomes and neonatal conditions after embryo transfer.**

Parameter	VD group (*n* = 300)	CS group (*n* = 600)	*P*
Caesarean delivery rate (%)	26.3%(79/300)	52,3%(314/600) [a]	
Twin-births rate (%)	11.3%(34/300)	5,0%(30/600)	
Full-term birth rate (%)	54.6%(164/300)	34.3%(206/600)	0.082
Pre-term birth rate (%)	7.7%(23/300)	8.3%(50/600)	0.082
Birth weight (g)	3104.7 ± 659.88	3227.0 ± 602.92	0.221
Low birth weight rate (%)	13.9%(25/180)	9.4%(12/127)	0.500

The delivery outcomes and neonatal conditions of the two groups after IVF/ICSI-ET were shown in Table 3. The collected information related to delivery outcomes of 900 women. Although the previous delivery of each woman was vaginal, the caesarean section rate after IVF/ICSI-ET was 26,3% in the VD group, the caesarean section rates were 52,3 %, in CS group. The difference in the caesarean section rate among the two groups was statistically significant (P<0.05). The twin delivery rate was 11.3% in the VD group and 5,0% in the CS group. Eighteen patients with multiple pregnancies underwent selective embryo reduction (10 cases in the VD group, 6 cases in the CS group). There were no differences in the full-term birth rate, preterm birth rate, birth weight, or low-birth-weight infant rate among the three groups. However, as shown in Table 3 the preterm birth rate was 7,7% in the VD group, and 8,3% in CS groups. Two cases of placenta previa occurred in the CS group. One case of placenta previa occurred in the CS group.

DISCUSSION

Our study indicated that IVF/ICSI pregnancies were associated with higher odds of caesarean section compared to spontaneous conceptions. The odds were also greater for elective caesarean sections compared to spontaneous conceptions than for emergent caesarean sections. This trend was also apparent, in IVF or ICSI, and fresh or frozen embryo transfer, compared to spontaneous conception. The rates of caesarean section differed among these countries, with high-income countries, showing increased rates during the past three decades (9). The type of health care system (public, private) was also associated with caesarean section rates, with private health systems cited as the most important structural factor in increased caesarean delivery (10,11). These same factors were associated with access to ART, with documented widespread disparities in access to ART between countries, and between private and public health care systems (12). In addition, our analysis included only observational studies and not randomized clinical trials (to our knowledge inexistent in this context) which might negatively influence the quality of the evidence. However, the large sample size of our pooled analysis and long observation periods overcame these limitations.

Multiple gestations are more common in IVF due to the transfer of multiple embryos to increase implantation chances. Twins and higher-order pregnancies are strongly associated with increased CS rates due to complications such as preterm labor, malpresentation, and intrapartum fetal distress. In our study, all twin pregnancies were delivered by caesarean section, which was consistent with global trends. These results are consistent with other studies showing that ART pregnancies are more likely to result in multiple gestations and malpresentation, two conditions that are highly suggestive of a caesarean delivery (3,4).

The results showed that pregnancies conceived by the IVF method had a significantly higher incidence of cesarean section compared to spontaneously conceived pregnancies. The most common reasons for elective cesarean sections were a previous cesarean section and an unfavorable position of the fetus. The findings were in line with earlier researches that indicated similar trends in Europe and the world. Recommendation was to promote vaginal delivery when medically justified, with an individual approach to each pregnant woman.

Previous studies had provided reliable evidence that women who conceive through assisted reproduction were more likely to choose caesarean section, which increased the caesarean section rate (13,14). In our study, although the previous mode of delivery was vaginal in the VD group, the caesarean section rate after IVF/ICSI-ET was 26.3%; however, in the CS groups, cesarean rates were 52.3%. One possible reason for this finding was the increased incidence of obstetric and perinatal complications that increased the likelihood of needing a cesarean section (15). Other possible reasons were that the high risk of IVF pregnancy, the "precious baby" effect, and maternal preferences in the absence of medical indications played an important role in the decision (16). In addition, it should be noted that the high rate of twin births after IVF treatment is also one of the reasons for the increased cesarean section rate. Our study also showed that twin delivery rate was 11.3% in the VD group and 5.0% in the CS group. Eighteen patients with multiple pregnancies underwent selective embryo reduction (10 cases in the VD group, 6 cases in the CS group). There were no differences in the full-term birth rate, preterm birth rate, birth weight, or low-birth-weight infant rate among the three groups.

CONCLUSION

This retrospective study found that the incidence of caesarean section among IVF pregnancies at the Clinical Center University of Sarajevo was substantially elevated, with 76% of women delivering by surgical means. Obstetric difficulties, previous cesarean delivery, fetal malpresentation, and multiple gestations were all contributing factors. The results highlighted the significance of rigorous prenatal monitoring and labor management techniques targeted at promoting safe vaginal deliveries when clinically suitable, even though caesarean delivery is frequently medically justified in ART pregnancies. Region-specific data, such as that presented in this study, were essential for guiding patient counseling, optimizing delivery planning, and informing public health strategies aimed at reducing unnecessary surgical births among women undergoing assisted reproduction.

REFERENCES

1. World Health Organization. Infertility definitions and terminology [Internet]. Geneva: WHO; 2019 [cited 2025 November 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/infertility.
2. Choe J, Shanks AL. In vitro fertilization. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2025 November 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560754/.
3. Sunderam S, Kissin DM, Crawford SB, Folger SG, Jamieson DJ, Barfield WD. Assisted reproductive technology surveillance United States, 2015. MMWR Surveill Summ. 2018;67(3):1-28. doi:10.15585/mmwr.ss6703a1.
4. Lodge-Tulloch NA, Elias FTS, Pudwell J, Boucoiran I, Demirtas E, Smith GN. Caesarean section in pregnancies conceived by assisted reproductive technology: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2021;21(1):244. doi:10.1186/s12884-021-03711-x.
5. Bermudez-Tamayo C, Fernández Ruiz E, Pastor Moreno G, Maroto-Navarro G, García-Mochón L, Pérez-Ramos FJ, et al. Barriers and enablers in the implementation of a program to reduce cesarean deliveries. Reprod Health. 2017;14(1):106. doi:10.1186/s12978-017-0369-3.
6. Huang J, Lin J, Cai R, Lu X, Song N, Gao H, et al. Effect of a prior cesarean delivery on pregnancy outcomes of frozen-thawed embryo transfer: A retrospective cohort study in a freeze-all setting. Acta Obstetricia et Gynecologica Scandinavica. 2020;99(10):1303-10. doi: 10.1111/aogs.13863
7. Wang L, Yao W, Tang X, Yao H, Wei S, Huang J, et al. Fertility outcomes of IVF/ICSI after caesarean section: a cohort study. Reproductive BioMedicine Online. 2020;40(5):719-28. doi: 10.1016/j.rbmo.2019.12.004
8. Patounakis G, Ozcan MC, Chason RJ, Norian JM, Payson M, DeCherney AH, et al. Impact of a prior cesarean delivery on embryo transfer: a prospective study. Fertility and sterility. 2016;106(2):311-6. doi: 10.5653/cerm.2023.06163
9. Vogel JP, Betran AP, Vindevoghel N, Souza JP, Torloni MR, Zhang J, et al. Use of the Robson classification to assess caesarean section trends in 21 countries: a secondary analysis of two WHO multicountry surveys. Lancet Glob Health. 2015;3(5):e260-e70. doi: 10.1016/S2214-109X(15)70094-X.
10. Bhatia M, Banerjee K, Dixit P, Dwivedi LK. Assessment of variation in cesarean delivery rates between public and private health facilities in India from 2005 to 2016. JAMA Netw Open. 2020;3(8):e2015022. doi: 10.1001/jamanetworkopen.2020.15022.
11. Sk R. Does delivery in private hospitals contribute largely to caesarean section births? A path analysis using generalised structural equation modelling. PLoS One. 2020;15(10):e0239649. doi: 10.1371/journal.pone.0239649.
12. Chambers GM, Sullivan EA, Ishihara O, Chapman MG, Adamson GD. The economic impact of assisted reproductive technology: a review of selected developed countries. Fertil Steril. 2009;91(6):2281-94. doi: 10.1016/j.fertnstert.2009.04.029.
13. Reubinoff BE, Samueloff A, Ben-Haim M, Friedler S, Schenker JG, Lewin A. Is the obstetric outcome of in vitro fertilized singleton gestations different from natural ones? A controlled study. Fertil Steril. 1997;67(6):1077-83. doi: 10.1016/s0015-0282(97)81442-2.
14. Sullivan EA, Chapman MG, Wang YA, Adamson GD. Population-based study of cesarean section after in vitro fertilization in Australia. Birth. 2010;37(3):184-91. doi: 10.1111/j.1523-536X.2010.00405.x.
15. Qin J, Liu X, Sheng X, Wang H, Gao S. Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: a meta-analysis of cohort studies. Fertil Steril. 2016;105(1):73-85.e1-6. doi: 10.1016/j.fertnstert.2015.09.007.
16. Srebnik N, Miron-Shatz T, Rolison JJ, Hanoch Y, Tsafrir A. Physician recommendation for invasive prenatal testing: the case of the 'precious baby.' Hum Reprod. 2013;28(11):3007-11. doi: 10.1093/humrep/det354.

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Determinants of Subjective Age in Recreationists in Serbia in Relation to Chronological Age, Personality Dimensions and Health

Determinante individualnog uzrasta rekreativnih vežbača u Srbiji u relaciji na hronološko doba, dimenzije ličnosti i zdravlje

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ABSTRACT

The aim of this cross-sectional study was to examine the relative contribution of predictors (chronological age, personality dimensions from the "Big Five" model, and health) to the variance of criteria (cognitive, comparative, and desired age). The pertinent sample of the online survey (N = 250) included recreationists of both sexes, aged 20 to 65, from the territory of the Republic of Serbia. The average age of the participants was (Myears = 42.15, SDyears = 1.12). The following measuring instruments were applied: The International Personality Item Pool (IPIP50), as well as variables that include aspects of subjective age and self-assessment of health. The calculated Cronbach's alpha coefficients showed satisfactory internal consistency reliability, so the instruments used can be operationalized on the Serbian population. The results of the study suggested that the cognitive and desired age of the participants was, on average, significantly lower than their chronological age, with the majority perceiving themselves to be younger than their peers in their own age group. The calculated Pearson correlation coefficients between the tested variables of chronological age, self-perception of health, and the Big Five personality dimensions generally range between low and moderate intensity. The findings of hierarchical regression analyses, with a significance level ($p \leq 0.05$ or $p \leq 0.01$) and a modest, but significant percentage of variance, indicated that the independent variables: chronological age, personality dimensions from the five-factor model, and self-concept of health are effective determinants of subjective age. The theoretical contributions and practical implications of the results, as well as limitations and suggestions for future longitudinal research, are discussed in the paper.

Keywords: recreationists, personality dimensions, subjective age, health

SAŽETAK

Cilj ove transverzalne studije bila je provera relativnog doprinosa prediktora (hronološkog doba, dimenzija ličnosti iz modela „Velikih pet" i zdravlja) na varijansu kriterijuma individualnog uzrasta (kognitivno doba, komparativno doba i željeno doba). Prigodni uzorak online istraživanja (N = 250) obuhvatio je rekreativne vežbače oba pola, od 20 do 65. godine, sa teritorije Republike Srbije. Prosečna starost ispitanika iznosila je (Mgodine = 42.15, SDgodine = 1.12). Primenjeni su merni instrumenti: Upitnik ličnosti (IPIP50), kao i varijable koje podrazumevaju aspekte individualnog uzrasta i samoprocenu zdravlja. Izračunati Kronbahovi alfa koeficijenti su pokazali zadovoljavajuću pouzdanost interne konzistencije. Stoga se oni mogu operacionalizovati i na srpskoj populaciji. Nalazi hijerarhijskih regresionih analiza sugerisali su da su prediktorske varijable (dimenzije ličnosti iz petofaktorskoga modela) efikasnije determinante individualnog uzrasta u relaciji s samoprocenom zdravstveng statusa. Takođe, dimenzije ličnosti i zdravstveni statu su, posle kontrole hronološog uzrasta, uz pripadajuće standardne greške predikcije, na nivou značajnosti ($p \leq .01$ ili $p \leq .05$), objasnili minimalnu proporciju varijanse tri prediktora individualnog uzrasta. U radu se razmatraju teorijski doprinosi i praktične implikacije rezultata, kao i ograničenja i predlozi za buduća longitudinalna istraživanja.

Ključne reči: rekreativci, kognitivni uzrast, komparativni uzrast, željeni uzrast, zdravlje

INTRODUCTION

Regardless of the fact that chronological age is a fundamental variable in empirical studies, the variable subjective age, i.e. the degree of self-assessment of one's own age, represents a relevant developmental characteristic. The construct of subjective age is a complex phenomenon that encompasses dimensions such as: perception of one's own age, constitution and behavior, identification of a person with another age group, or assessment of desired age, regardless of one's actual age (1). According to the assumptions of subjective age, the methods of its examination also differ (2). Research (3) has shown that subjective age, compared to chronological age, is a more effective determinant of psychological and physical functioning in the elderly population. Subjective age more effectively than chronological age guides how adults experience their social roles, which in turn contributes to a clearer understanding of their manifestations (4). In addition, subjective age is a relevant determinant of life expectancy in older adults (5). Empirical studies have found that the majority of the adult population perceives themselves as younger than their chronological age and that the difference between subjective and chronological age increases in the older population (6). One gets the impression that most people at the beginning of adulthood, around the age of 20, feel somewhat older, while those over three decades old feel younger than their chronological age. The tendency of the older population to feel younger is theoretically explained by the denial of aging as an implication of fear of aging, or a defence mechanism (7). Maintaining a youthful age identity is interpreted as a model of self-assurance that influences personal well-being, life satisfaction, and self-esteem of adults, and is therefore characteristic of subjective cultures that exalt youth (8). The majority of studies report that negative models of aging and fear of it are not relevantly correlated with the subjective age of adults (9,10), which does not support the previous interpretation of the trend of adults to perceive themselves as younger. The second, current aspect of general development interprets the difference between subjective and chronological age as the result of the coordination and adaptation of one's own age experiences that condition the perception of personal age (11). The interaction of subjective age and socio-demographic characteristics has usually been tested with differentiated indicators of psychological functioning and health status, with relevant gender differences in subjective age generally not defined (12). Health variables have the greatest impact on the proportion of variability in the subjective age construct, with poorer health contributing to higher subjective age, and younger age group membership being correlated with more efficient physical functioning and spiritual health, as well as with more optimal self-perception of health status (13).

In the first decade of the 21st century, a large number of studies have examined the contribution of personality to the perception of subjective age. The authors (14) emphasize that the traits of extraversion and openness to new experiences are correlated with younger subjective age in the middle-aged population. Research authors (15) found in a sample of older adults that none of the "Big Five" personality dimensions contribute significantly to the difference between subjective and chronological age, except for a minimal proportion of the variance of extraversion. In the study (16) they found an interaction between self-perception of health status and subjective age in middle-aged, but not younger adult populations, with extraversion being correlated with younger subjective age in older adults, and openness to experience in middle-aged and older adults. However, the personality dimensions conscientiousness, neuroticism, and agreeableness are not in cohesion with subjective age in older age groups, while conscientiousness in the younger adult group is in cohesion with older age.

Researchers have found that positive self-perceptions of health status and personality dimensions (i.e., extraversion and openness), which are typically attributed to younger people, have a relevant contribution to the perception of a younger subjective age. In addition, the study (17) emphasizes that younger subjective age correlates with later personality changes, i.e. an increase in the levels of openness, conscientiousness, and agreeableness dimensions.

Given the lack of empirical studies of the construct of subjective age in Serbian adult participants, the aim of this research was to examine predictors of subjective age (cognitive, comparative and desired age) and their interaction in adult recreationists in the Serbian-speaking area. Cognitive age is based on the following aspects: how old a person feels, how old they look, how old they are based on their work, behavior, and interests. Comparative age involves an individual comparison of personal chronological age in relation to other members of the age group. Desired age assumes how old a person wants to be. Based on the defined aim of the research, two alternative hypotheses were tested in this paper. It is assumed that the variable chronological age is a statistically significant and positive determinant of cognitive age (H_1). It is expected that the dimensions of the five-factor personality model (extraversion, emotional stability, and openness) are statistically significant negative predictors of comparative age, and the dimensions (conscientiousness and emotional stability) are significant positive predictors of desired age and It is assumed that the predictor of self-assessment of health is not a statistically relevant determinant of the desired age criterion (H_2).

MATERIALS AND METHODS

Participants and research procedure

The pertinent sample (N = 250) consisted of recreationists of both sexes from different cities in the Republic of Serbia, with an age range of 20 to 65 years (Wwomen = 128 and Mmen = 122). The average age of the participants was (M = 40.23, SD = 11.46 years). All participants had at least one year of organized recreational training processes, lasting at least twice a week. The criterion for selecting participants was the use of social networks.

The link to the survey measuring instruments was shared via e-mail addresses available from personal contacts and social networks. After providing informed consent, participants were asked to forward the digital version invitation to participate other people via online techniques using the platform (Google Forms). Measuring instruments were available on social group websites, electronic participation in the research was voluntary, without financial compensation. The electronically completed (online) battery of measuring instruments could not be correlated with the identity of the participants who completed them, because instead of their names and e-mail addresses, they entered their passwords using all available characters. At the beginning of the research, participants were given a brief explanation in electronic form about how to respond, and they could withdraw at any time without any consequences. The survey lasted about 20 minutes. The research was conducted in December 2024, and was approved by the Ethics Committee of the Serbian Academy of Innovation Sciences in Belgrade.

Sample variables (measuring instruments)

Three measuring instruments were used in the research: a questionnaire on individual socio-demographic characteristics (gender, age, level of education), which includes three aspects of subjective age (14), a questionnaire on general health status created specifically for the needs of this research in which participants respond by marking one of the offered answers, as well as the IPIP50 personality questionnaire for examining personality dimensions from the five-factor model.

Measurements of subjective age

Cognitive age is based on four dimensions of personal perception of age, considering the individual's feelings, appearance, behavior and interests (19). On a five-point scale (1 = *much younger,* 2 = *younger*, 3 = *about the same,* 4 = *older* and 5 = *much older*), participants assessed how old they felt in relation to most people their age, how they looked in terms of age, how old they felt based on their work, behavior and interests – regardless of their actual chronological age. The overall measure of cognitive age is calculated as the mean value of the four dimensions. The resulting difference (in years) between chronological and cognitive age represents a measure of recreational age. The internal consistency reliability (Cronbach alpha) is 0.76.

Comparative age is based on a partial comparison of one's chronological age with other members of one's own age group. Participants circle one of the answers to the question of whether they feel much younger, the same, older, or much older than most people their age. Responses are given on a five-point Likert scale, where 1 means younger all the time, 2 – younger most of the time, 3 – neither younger nor older, 4 – older most of the time, and 5 means – older all the time.

Desired age was assessed by asking the question "How old would you like to be?", and the answer was expressed in years. The difference between chronological and desired age was calculated as a measure of age gap.

Health. Personal assessment of overall health status was examined using the question "How would you rate your current health?" Participants responded on a five-point Likert scale to assess their own health (1 = extremely poor to 5 = excellent).

The personality questionnaire – IPIP50 (15) examines the five major personality dimensions from the Big Five five-factor model. The IPIP5050 includes 50 items, 10 positively and negatively formulated statements for each of the five fundamental personality dimensions (extraversion, conscientiousness, agreeableness, emotional stability and openness to experience or intellect). The participant is tasked with indicating for each item on a five-point Likert-type scale how much it applies to them (1 = *completely false,* to 5 = *completely true*). An example of a statement on the extraversion scale is "I talk to a lot of different people at parties", for agreeableness "I am sensitive to other people's feelings", for conscientiousness "I do housework right away", for neuroticism "I am often sad" or "I get stressed easily", and for intellect "I spend my time thinking". The total score is formed as the average of the assessments of all statements, with negatively formulated items being scored in reverse. The internal consistency coefficients – Cronbach's alpha of individual subscales of the "Big Five" in this study showed satisfactory metric characteristics: $\alpha_{extraversion}$ = .75, $\alpha_{agreeableness}$ = .79, $\alpha_{conscientiousness}$ = .80, $\alpha_{emotional\ stability}$ = .82 and $\alpha_{openness}$ = 0.74.

Statistical analysis

The data processing method in this cross-sectional study was performed using descriptive and analytical statistics. The correlation between manifest variables was assessed using Pearson correlation methods, with an initial level of statistical significance of $p \leq 05$, while the correlations between predictor and criterion variables were analyzed using hierarchical regression analysis. The data were processed using the IBM SPSS Statistics for Windows software package (Corp., Armonk, N.Z., USA).

RESULTS

Descriptive statistics

The basic central and dispersive parameters and measures of the shape of the data distribution for chronological age and three indicators of subjective age are shown in Table 1 to check the prerequisites for further parametric analysis.

Table 1 **Basic descriptive statistics and values of the shape of the distribution of results on the applied variables.**

Variables	*M*	*SD*	Range	*Sk*	*Ku*
Chronological age	45.01	12.40	19-69	.19	.45
Cognitive age	40.00	10.05	15-80	.56	.34
Comparative age	2.40	.68	1-5	.48	.62
Desired age	32.73	12.10	1-68	.37	.50

Legend: M = arithmetic mean; SD = standard deviation; Sk = skewness; Ku = kurtosis, Standard error value (SE) of indicator Sk is 0.11, and of Ku is 0.22.

Based on the empirically calculated arithmetic means in the descriptive matrix, it is observed that the participants on average have a maximally expressed chronological age (M = 45.01), and a minimally expressed comparative age (M = 2.40), while the maximal variability of the results was achieved on the variable (chronological age = 12.40), and minimal on the variable (comparative age = .68). The obtained skewness and kurtosis scores of the distribution of the observed variables are not outside the range of ±2, which is a prerequisite for conducting subsequent statistical multivariate analyses (16).

In order to test the direction and intensity of the co-dependence of subjective age in the total sample, Pearson correlation coefficients (Pearson's r) with three measures of subjective age were calculated in Table 2, controlling for the chronological age of the participants.

Table 2 **Significance of intercorrelation of subjective age variables, personality dimensions and self-assessment of health.**

Variables	1	2	3	4	5	6	7	8	9
1. Cognitive age	–								
2. Comparative age	.05	–							
3. Desired age	.63**	-.01	–						
4. Extraversion	-.29**	-.20*	-.32**	–					
5. Agreeableness	-.30**	-.03	-.06	.28**	–				
6. Conscientiousness	-.20*	-.02	.30**	.07	.40**	–			
7. Emotional stability	-.03	-.18*	.05	.31**	.17*	.03	–		
8. Openness	-.39**	-.08	-.29**	.29**	.34**	.01	.08	–	
9. Self-assessment of health	-.27**	-.30**	-.20*	.30**	.21*	.02	.40**	.20*	–

Annotation: p -= statistical significance *p ≤ 0.05. **p ≤ 0.01.

Looking at the correlation matrix, it can be seen that the values of the linear correlation coefficients of the measured variables mainly range between low or moderate intensity, from .17 to .63. The obtained results show that the measured variable cognitive age is stochastically significant from low to moderate intensity and bivariately correlated with all "Big Five" personality dimensions, except for the emotional stability dimension. Cohesion with personality traits (extraversion, agreeableness, and openness to experience) showed a negative trend, with more prominent extraversion, agreeableness, and openness being correlated with lower cognitive age. However, the association between cognitive age and the conscientiousness dimension was shown to be in a positive direction, suggesting a higher cognitive age in more conscientious participants. The variable comparative age is significantly, and negatively with relatively low intensity, correlated only with perceived personality dimensions (extraversion and emotional stability), emphasizing the tendency for more extraverted and emotionally stable individuals to perceive themselves as younger than their peers. The desired age variable is negatively and conditionally with low intensity relevant in its relationship with the dimensions of extraversion and openness, indicating a lower desired age in more extraverted individuals and those more open to new experiences. Moreover, the interaction with the conscientiousness dimension is positive and low, but statistically significant, suggesting that more conscientious participants report a higher desired age. In the context of the cohesion of subjective age measures with the self-assessment of health variable, it was defined that the tested health status of individuals is significantly and negatively correlated with conditionally low intensity with three indicators of subjective age, which draws attention to better health in younger individuals. It was shown that the correlations between self-concept and personality dimensions varied from zero correlations to moderate ones.

For example, the perceived personality dimension of agree ableness is in a relevant positive and moderate interaction with the other four dimensions, with the dimension of conscientiousness being in a significant co-dependence only with the dimension of agreeableness. Finally, the correlation matrix found that the examined variable, self-assessment of health, was statistically significantly and with low to moderate intensity in bivariate correlation with all "Big Five" personality dimensions, except for the conscientiousness dimension, indicating a more optimal perception of health status in people with more prominent extraversion, agreeableness, openness, and emotional stability.

In order to examine the relative contribution of predictors: subjective age measures – chronological age (first model), personality dimensions from the five-factor model (second model) and self-assessment of health (third model) in explaining the variance of the criteria: cognitive age, comparative age and desired age in Table 3, three multivariate hierarchical regression analyses were conducted. Before that, in order to satisfy the assumptions for calculating hierarchical regression, a diagnosis of potential bivariate multicollinearity among the predictors was performed. First, the indicators were checked: the Tolerance test, which represents the proportion of the standard variance that is not explained by the remaining variables, and then the Variance Inflation Factor □ VIF, which represents the proportion of the total standard variance and the tolerance value. Since it was determined that the T values were less than 0.1, and no VIF value was greater than 10, it was concluded that they were within acceptable values, because no predictor variable showed harmful multicollinearity, so the reliability of the linear regression model is not questionable for processing the data of this study (17).

Table 3 **Hierarchical regression analysis for cognitive, comparative and desired age criteria.**

Variables	*M*	*SD*	Range	Sk	*Ku*
Chronological age	45.01	12.40	19-69	.19	.45
Cognitive age	40.00	10.05	15-80	.56	.34
Comparative age	2.40	.68	1-5	.48	.62
Desired age	32.73	12.10	1-68	.37	.50

Legend. β = standardized regression beta coefficient; β SE = standard error of prediction (in brackets); R^2 = coefficient of multiple determination-total variance; βR^2 = contribution/change in the proportion of explained variance after introducing a new/additional block of predictor variables; Ftest = relationship between predictor values; **p ≤.01. * p ≤ .05.

In the first step of the analysis, chronological age independently explains 4% of the square of the deviation of individual results from the arithmetic mean – the variance of cognitive age, with the control variable (chronological age) being a statistically significant independent positive predictor. By introducing the Big Five predictor group (the personality dimension of the five-factor model) into the equation of the second model, an additional 8% of the significant deviation - variability of the comparative age criterion was explained, with the obtained beta coefficients showing that the independent/control variables (extraversion and agreeableness) are significant negative predictors of cognitive age. In the third and last model, introducing the predictor of self-assessment of health explained an additional 5% of the variance in the criteria. Based on the obtained linear function, it is concluded that the tested set of predictor variables explains between 4 and 17% of the common variance in the three forms of subjective age, which indicates that the used independent variables (chronological age, personality dimensions and self-assesment of health) are relevant in predicting subjective age criteria. The combination of all control variables used in the definitive regression model, along with the associated standard errors of prediction and the stochastically significant F ratio, explained 17% of the significant mean square dispersion – the variability of the subjective age criteria, so the variables are also significant in predicting the tested criteria.

Based on the results of the hierarchical regression, it is concluded that both tested alternative hypotheses were confirmed: it is expected that the dimensions of the five-factor personality model (extraversion, emotional stability, and openness) are statistically significant negative predictors of comparative age, and the dimensions (conscientiousness and emotional stability) are significant positive predictors of desired age (H_1), and it is also expected that the predictor of self-assessment of health is not a statistically relevant determinant of the desired age criterion (H_2).

DISCUSSION

The aim of this empirical study was to examine the relationships between criterion variables of subjective age (cognitive, comparative and desired age), as well as their interactions with the dimensions of the five-factor model of personality and health in a sample of Serbian recreational athletes in adulthood.

Results in studies have shown that the correlation of predictor variables and health explains the maximum proportion of subjective age variability (18). Younger age identity is in cohesion with better physical and spiritual health status (19). Also in this study, as expected, the estimate of the predictor variable health, controlling for chronological age, is statistically significantly, negatively and relatively weakly correlated with the criterion variables (cognitive and comparative age), but not with the criterion desired age.

This draws attention to the trend that individuals who perceive their health status more optimally perceive themselves as younger based on their appearance, behavior and interests, as well as feeling younger compared to members of their own age group.

The findings of multivariate hierarchical regression analyses indicated that the self-concept dimension of personality from the Big Five five-factor model, after controlling for chronological age, is a more efficient determinant of the three criterion variables of subjective age than a predictor of self-rated health. The proportion of variability in subjective age explained by self-rated health, after controlling for chronological age and the construct of the "Big Five" personality dimensions, was 0% for cognitive, 4% for comparative, and 4% for desired age. The findings are not redundant with the results of previous research, which showed that the independent variable self-rated health explains a large percentage of the variability in subjective age (20). The consequence of these distinctions is probably methodologically generated, which involves the methods of examining subjective age and sample variables. The sample of participants in this study has a significant age range, with a more intense association of health variables and subjective age primarily defined in older participants.

Also, the proportion of variability - squared standard deviations that, after controlling for chronological age, explained personality dimensions was 12% for cognitive, 17% for comparative, and 18% for desired age. In addition, personality traits (extraversion and agreeableness) were shown to be relevant negative determinants of cognitive age, and extraversion, emotional stability and openness to experience were significant negative determinants of comparative age, while conscientiousness and emotional stability were significant positive predictors of desired age. Although the correlation analysis defined a statistically significant positive relationship between conscientiousness and a relevant negative relationship between openness and cognitive age, these two personality traits did not prove to be significant determinants of cognitive age in the regression functions. At the same time, the dimensions of extraversion and openness were relevantly – in a negative direction – associated with the desired age, while they were not defined as significant determinants in the hierarchical regression analyses.

The interactions of the personality traits of extraversion and openness to new experiences with younger age identification in cognitive and comparative age can be explained by the fact that their characteristics, e.g. assertiveness, excitement seeking, sociability, etc. (for extraversion) and the tendency to seek new ideas, intellectual curiosity, unconventional attitudes, etc. (for openness), are most often attributed to younger individuals (21).

The aforementioned authors emphasize that as they age, extraverted and open individuals, through the process of social comparison of personal behaviors with peers and in reaction to age-related changes in personality dimensions, increasingly distance themselves from their own age group and perceive themselves as more identical to younger age groups. In research (22), it was found that the trait of openness to experience is correlated with younger individual age, because older open individuals tend to distance themselves from their peers.

The finding that implies the influence of the conscientiousness dimension on the desired age coincides with some earlier results and interpretations, according to which conscientiousness is an indicator of psychosocial maturity, especially in the transition to adulthood, and this personality trait interacts with higher subjective age (23). Also, participants more often evaluate the attribute of conscientiousness in older people, in accordance with age-related personality stereotypes (24). Therefore, more conscientious individuals, compared to less conscientious ones, want to be older because the characteristics of conscientiousness, e.g. dedication to work, responsibility, self-discipline, etc., are considered characteristics of a more mature age. In addition, it has been observed that a more manifest self-concept of neuroticism contributes to a lower level of desired age. The likely reason for this is that more neurotic individuals manifest a more negative attitude towards personal age and probably have a harder time coping with the aging process (25). However, higher levels of emotional stability contributed to a lower comparative age, with a trend for more emotionally stable individuals to be perceived as younger than their peers. It is likely that more emotionally stable individuals cope with stress more effectively, and their more positive emotional states positively affect well-being, which contributes to them feeling younger.

In most studies on the relations between the agreeableness dimension from the five-factor model of personality dimensions and subjective age, no correlation was found (30, while this research showed that agreeableness is in a stochastic interaction with younger cognitive age. It is likely that individuals with more manifest Big Five agreeableness traits are more satisfied with their social relationships, which positively reflects on their well-being, and indirectly on their younger cognitive age. Nevertheless, it is concluded, regardless of cross-cultural differences, that the findings of this study, which relate to the relations between personality dimensions and subjective age, are largely consistent with the findings of research (26) which suggest that personality demands attention as a determinant of individual age, independent of the predictor variable of health.

In general, some methodological limitations in this research should be taken into account. The first limitation relates to the correlational design of the research, which does not allow conclusions to be drawn about cause-and-effect interactions between variables. For example, subjective age probably contributes to the prediction of health status, despite the fact that in most studies, including this one, the predictor health is observed as a determinant of subjective age, with the expectation that poorer health status causes an individual to feel older than they actually are. Also, since the percentage of variability in the three criterion variables of subjective age predicted by personality dimensions and self-rated health was relatively minimal, future empirical studies with a longitudinal design should also focus on other possible independent variables of individual age, as well as possible regulators of the relationships between the Big Five personality dimensions and subjective age, such as individual well-being, fear of aging, age-normative events, lifestyle, vitality, etc. In doing so, the influence of personality dimensions and health status in different age groups should be compared, which was not examined in this research.

In fact, the results of the research on this pertinent sample show that chronological age can regulate the relationships between subjective age, health, and personality dimension constructs, and with increasing age, health status and personality dimensions have a greater contribution to the perception of personal age.

REFERENCES

1. Denche-Zamorano A, Salas-Gómez D, Franco-García JM, Adsuar JC, Parraca J. Collado-Mateo D. Associations between Physical Activity Frequency in Leisure Time and Subjective Cognitive Limitations in Middle-Aged Spanish Adults: A Cross-Sectional Study. Healthcare. 2022;12(11):1056-65. doi: 10.3390/healthcare12111056.
2. Suberry A, Bodner E. Psychological Well-Being and Self-Aging Attitudes Moderate the Association between Subjective Age and Age Discrimination in the Workplace. Behav Sci (Basel). 2024;14(9):742-53. doi: 10.3390/bs14090742.
3. Iwano S, Kambara K, Aoki S. Psychological interventions for well-being in healthy older adults: Systematic review and meta-analysis. J Happiness Stud. 2022;23:2389-2403. https://doi.org/10.1007/s10902-022-00497-3
4. Hasan SS, Khan A. Saher N. Perception of ageing among literate urbanite women in islamabad: how education, professional and digital exposure influence on perception. Sociology & Amp; Cultural Research Review. 2025;3(1):148-82.
5. Allen JO, Solway E. Singer MD, Jeffrey T, Moise V. Malani PN. Experiences of Everyday Ageism and the Health of Older US Adults. Jama Netw Open. 2022;5(6):e2217240. doi.org/10.1080/16078055.2024.2351077.
6. Butson M, Jeanes R, O'Connor J. Experiences of Older Adults Leisure-Time Physical Activity in Aquatic and Leisure Facilities. World Leisure Journal. 2024;67(1):1-21. doi.org/10.1080/16078055.2024.2351077
7. Pezzoli S, Giorgio J, Martercek A, Dobyns L, Harrison TM, Jagust WJ. Successful cognitive aging is associated with thicker anteriorcingulate cortex and lower tau deposition compared to typical aging. Alzheimers Dement. 2024;20(1):341-55. doi: 10.1002/alz.13438.
8. Wodarz R, Rogowska AM. The Moderating Effect of Body Appreciation on the Relationship between Self-Esteem and Life Satisfaction. Eur J Investig Health Psychol Educ. 2024;14(4):870-87. doi: 10.3390/ejihpe14040056.
9. Carstensen LL. Socioemotional selectivity theory: the role of perceived endings in human motivation. Gerontologist. 2021;61(8):1188-96. doi: 10.1093/geront/gnab116.
10. Hu M, Wu H, Qiu, S. Life Satisfaction Among Chinese Aged Workers: Interplay of Organizational Justice, Workplace Emotions, and Subjective Age Perception. Psychology Research and Behavior Management. 2024;17:23-37. doi.org/10.2147/PRBM.S440168.
11. Saraç F, Kılınç BB, Çelikel P, Büyüksefil M, Yazıcı MB. Derelioglu, SS. Correlations between Dental Age, Skeletal Age, and Mandibular Morphologic Index Changes in Turkish Children in Eastern Anatolia and Their Chronological Age during the Pubertal Growth Spurt Period: A Cross-Sectional Study. Diagnostics (Basel). 2024;14(9):887. doi: 10.3390/diagnostics14090887.
12. Işbilir Ş, Çiftçi ZZ, Karayılmaz H, Günen Y, Ilmaz, S. Is There Any Relationship between Pubertal Growth Spurt and Dental or Bone Age Estimation Methods? Australian Journal of Forensic Sciences. 2023;55(3):1-18. doi:10.1080/00450618.2022.2043435.
13. Pecchinenda A, Yankouskaya A, Boccia M, Piccardi, L, Guariglia, C, Giannini AM. Exploring the relationship between perceived loneliness and subjective cognitive decline in older individuals. Aging Ment Health. 2024;28(1):73-82. doi: 10.1080/13607863.2023.2242291.
14. Kaliterna-Lipovčan LJ, Prizmić-Larsen Z, Šakić V. Subjektivna dob, životno zadovoljstvo i zdravlje. Društvena istraživanja. 2002;11(6):897-908.
15. Mlačić B, Goldberg LR. An analysis of a cross-cultural personality inventory: The IPIP Big-Five factor markers in Croatia. Journal of Personality Assessment. 2007;88(2):168-77. doi: 10.1080/00223890701267993.
16. Kline RB. Principles and practice of structural equation modeling. New York: Guilford Publications; 2015.
17. Jovičić M, Mitrović-Dragutinović R. Ekonometrijski metodi i modeli. Beograd: Centar za izdavačku delatnost Ekonomskog fakulteta u Beogradu; 2018.
18. Ma L, Li L. The Impact of Leisure Sports Activities on the Psychological Health of The Public. Journal of Sport Psychology. 2024;33(3):62-72.
19. Chia JL, Hartanto A, Tov W. Retirement and life satisfaction among middle-aged and older adults: A piecewise growth mixture analysis. Psychol Aging. 2024;39(8):915-32. doi: 10.1037/pag0000853.

20. MacEwan JP, Chiu K, Ahmad NN, Sacks N, Shinde S, Poon JL, et al. Clinical, economic, and health-related quality of life outcomes in patients with overweight or obesity in the United States: 2016–2018. Obes Sci Pract. 2023;10(1):e726. doi: 10.1002/osp4.726.
21. Radwan EHM, Elmawla DA, Elsayed EBM. Effectiveness of Physical and Social Leisure Activities Program Participation on Feeling of Loneliness, Happiness and Self-Esteem among Institutionalized Elderly. Egyptian Journal of Health Care. 2024;15(1): 1728-44. doi: 10.21608/ejhc.2024.350817.
22. Adedeji A, Olonisakin TT, Buchcik J, Idemudia, ES. Socioeconomic status and social capital as predictors of happiness: evidence and gender differences. Humanities and social sciences communications. 2023;10(119):1-8. doi: 10.1057/s41599-023-01606-0.
23. Oladi E, Esfahani M, Azimkhani A, Shabnam ASAN. The Effect of Physical Activity and Selected Games in Leisure Time on the Feeling of Loneliness, Self-Efficacy, and Life Expectancy of Elderly Women. Akdeniz Spor Bilimleri Dergisi. 2023;6(2):670-81. doi: 10.38021/asbid.1227714
24. Crespo-Sanmiguel I, Zapater-Fajarí M, Garrido-Chaves R., Hidalgo V, Salvador A. Quejas subjetivas de memoria en jóvenes; su relación con el rendimiento cognitivo objetivo y el papel del neuroticismo. Annals of Psychology. 2024;40(2):323-34. DOI: 10.6018/analesps.557291.
25. Korolkiewicz M, Fewster-Young, N, Marmolejo-Ramos F, Gabriel F, Kariuki P, Puga JL, Marrone R, Miles A. Fear of the unknown: Relationship between statisticsanxiety and attitudes toward statistics of universitystudents in three countries. Teaching Statistics. 2025;47:17-38. doi: 10.1111/test.12381
26. Buchinger L, Entringer TM, Richter D, Wagner GG., Gerstorf D, Bleidorn W. Codevelopment of life goals and the Big Five personality traits across adulthood and old age. Journal of Personality and Social Psychology. 2024;126(2):346-68. doi.org/10.1037/pspp0000477

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The Association of Neoadjuvant Therapy with Postoperative Prolonged Air Leak in Patients after Lung Resections Up to the Level of Lobectomy Due to Non-Small Cell Lung Cancer

Povezanost neoadjuvantne terapije sa postoperativnim prolongiranim zračnim gubitkom kod kojih je učinjen resekcioni zahvat na plućima do nivoa lobektomije zbog dijagnosticiranog nemikrocelularnog karcinoma pluća

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ABSTRACT

Introduction: prolonged air leak (PAL) is a common post operative complication after lung resections in non-small cell lung cancer (NSCLC) patients. While impaired lung function is a key risk factor, the role of neoadjuvant therapy remains unclear. This study examines its potential influence on PAL. Aim: to investigate the correlation of neoadjuvant therapy and the presence of PAL in operated NSCLC patients. Materials and methods: a multicenter study included 168 adults with NSCLC who underwent lung resections up to lobectomy (2017-2020). Clinical data and postoperative outcomes were analyzed, with PAL defined as an air leak lasting more than six days. Results: the mean patient age at the time of NSCLC diagnosis was 64.45±7.36 years, with women significantly younger than men (p=0.015). Adenocarcinoma was the most common tumor type, occurring at a significantly higher frequency than expected (p<0.001). Neoadjuvant therapy was administered in 6.5% of patients, whereas no statistically significant association was found between neoadjuvant therapy and PAL. Conclusion: neoadjuvant therapy did not independently increase PAL risk, although its interaction with other factors warrants further investigation.

Keywords: non-small cell lung carcinoma, air leaks, pulmonary, neo adjuvant therapy

SAŽETAK

Uvod: prolongirani zračni gubitak (engl. prolonged air leak, PAL) predstavlja čestu postoperativnu komplikaciju nakon resekcija pluća kod pacijenata s nemikrocelularnim karcinomom pluća (engl. non-small cell lung cancer, NSCLC). Iako je narušena plućna funkcija ključni faktor rizika, uloga neoadjuvantne terapije ostaje nejasna. Ova studija ispituje njen potencijalni uticaj na PAL. Cilj: ispitati povezanost neoadjuvantne terapije i prisustva PAL-a kod operisanih pacijenata s NSCLC-om. Materijali i metode: multicentrična studija obuhvatila je 168 odraslih osoba s NSCLC-om koje su podvrgnute resekcijama pluća do nivoa lobektomije (2017–2020). Analizirani su klinički podaci i postoperativni ishodi, pri čemu je PAL definisan kao zračni gubitak duži od šest dana. Rezultati: prosječna dob pacijenata u vrijeme dijagnoze NSCLC-a bila je 64,45±7,36 godina, pri čemu su žene bile značajno mlađe od muškaraca (p=0.015). Adenokarcinom je bio najčešći histološki tip tumora, sa značajno većom učestalošću od očekivane (p<0.001). Neoadjuvantna terapija primijenjena je kod 6.5% pacijenata, dok nije utvrđena statistički značajna povezanost između neoadjuvantne terapije i PAL-a. Zaključak: neoadjuvantna terapija nije samostalno povećala rizik za PAL, iako njena interakcija s drugim faktorima zahtijeva daljnja istraživanja.

Ključne riječi: nemikrocelularni karcinom pluća, zračni gubitak, pluća, neoadjuvantna terapija

INTRODUCTION

Air leak is the most common postoperative complication that arises after lung resections in patients with non-small cell lung cancer (NSCLC) (1). In the majority of cases, it occurs due to the presence of an alveolopleural fistula, which is defined as a communication between the lung parenchyma distal to the segmental bronchus and the pleural space (2).

Prolonged air leak (PAL) is still a subject of debate in global literature, but the currently accepted definition states that prolonged air leak is any leak that lasts for 5 or more postoperative days, which is also the average length of hospital stay after lobectomy and lung resections of lesser extent (1-3). The most prominent risk factor for PAL is an impaired lung function, consistent with chronic obstructive pulmonary disease (COPD). Other risk factors include reduced diffusion capacity, upper lung resections or bilobectomy, the presence of pleural adhesions, a relatively low BMI, increased dyspnea score, concurrent pneumothorax, systemic steroid use, radiological signs of emphysema, as well as histological confirmation of emphysema (2-6).

There are also certain factors and conditions that are the subject of controversy and debate regarding their role in the development of PAL. One such factor that could be the subject of further research, but has so far remained somewhat overlooked in practice, is the use of neoadjuvant therapy. It has a multifactorial impact on the outcome of lung cancer treatment and has therefore been noted as a determinant that affects the early postoperative course in several ways. While there is no isolated impact of neoadjuvant therapy on prolonged air leak, several noticeable variations have been observed in the length of postoperative drainage in patients who previously received neoadjuvant chemotherapy.

AIM

The aim of this paper was to initiate a reasoned discussion on the extent of neoadjuvant therapy's influence on prolonged air leak following lung surgery for NSCLC. This is particularly relevant given the continued skepticism towards neoadjuvant therapy, despite the fact that its positive effects have already been practically demonstrated.

MATERIALS AND METHODS

For the purpose of this study, a multicenter research project was conducted at the Clinic of Thoracic Surgery, Clinical Center University of Sarajevo (CCUS), from 1 January 2017 to 30 June .2020. It included all patients over the age of 18 who underwent lung resections up to the level of lobectomy and were pathologically diagnosed with NSCLC. A total of 168 patients were included in the study.

For each patient, clearly defined data from their medical histories at the time of their hospital stay were analyzed.

The inclusion criteria for the study are as follows:

1. Operative lung resections up to the level of lobectomy, which include:
   a. Standard anatomical resections (lobectomies);
   b. Non-anatomical (wedge or atypical) resections.
2. Histopathologically confirmed NSCLC;
3. Patients older than 18 years of age.

Following the surgical procedure (lobectomy or wedge resection), two chest tubes are typically placed within the pleural cavity. One is directed to the apex of the pleural cavity and serves to remove air from it, while the other is positioned lower, toward the phrenicocostal sinus, primarily to remove the fluid.

The criteria for postoperative chest tube removal include complete pulmonary re-expansion confirmed on chest radiography under conditions of passive (underwater) drainage without active suction, absence of detectable air leakage, and a daily drainage volume of less than 100 mL over 24 hours.

The threshold value for confirming the presence of an air leak in this study is the presence of a chest tube for more than 6 postoperative days.

RESULTS

A total of 168 patients were included in this study. All had histopathologically confirmed NSCLC and underwent surgical lung resection up to the level of lobectomy at the Clinic of Thoracic Surgery, Clinical Center University of Sarajevo, between 1 January 2017 and 30 June 2020. Patients were followed from hospital admission through the entire hospitalization period until discharge from the clinic. Among the study cohort, 108 (64.3%) were male and 60 (35.7%) were female.

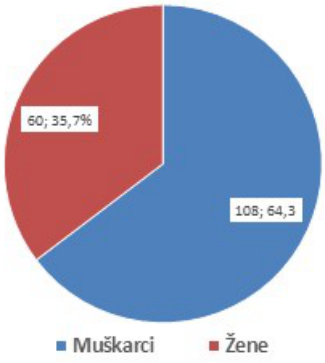

Figure 1 **Gender distribution of patients with NSCLC who underwent lung resection up to the level of lobectomy (N=168).**

Table 1 **Distribution of patients diagnosed with non-small cell lung carcinoma (NSCLC) who underwent lung resection up to the level of lobectomy, according to age groups and gender (n=168).**

Variable	Total	p-value	Men	Women	p-value
Age (mean ± SD)	64.45±7.36	-	64.36±7.36	61.20±9.60	[a]p=0.015*
Age groups (n;%)					
<50	7 (4.2%)	[b]0.000*	3 (42.86%)	4 (57.14%)	[b]0.232
50-59	42 (25.0%)		22 (52.38%)	20 (47.62%)	
60-69	78 (46.4%)		54 (69.23%)	24 (30.77%)	
70-79	38 (22.6%)		27 (71.05%)	11 (28.95%)	
≥80	3 (1.8%)		2 (66.67%)	1 (33.33%)	
Total	168 (100.0%)		108 (64.34%)	60 (35.7%)	-

a Independent samples t-test; b Pearson Chi-square test; *two-tailed test at a significance level of p<0.05

The mean age of patients diagnosed with NSCLC was 64.45 ± 7.36 years. Stratified by gender, the mean age of male patients was 64.36 ± 7.36 years, whereas female patients had a mean age of 61.20 ± 9.60 years, representing a statistically significant difference in mean age between genders ($p = 0.015$).

With respect to age distribution, slightly less than half of the cohort, 78 patients (46.4%), was in the 60-69-year age group. The observed frequencies across age groups differed significantly from those expected ($p < 0.001$).

Analysis by gender within age groups indicated that male patients predominated in all age categories except for the <50-year group. In the 60–69-year age group, which was the most represented, males accounted for 54 of 78 patients (69.23%), while in the 70–79-year group, males represented 27 of 38 patients (71.05%). However, the differences between observed and expected frequencies by age and gender were not statistically significant ($p = 0.232$) (Table 1).

Table 2 **Distribution of lung cancer types in patients who underwent lung resection up to the level of lobectomy (n=168).**

Type of lung cancer	n	%	p-value
Adenocarcinoma	86	51.2	[a]0.000*
Carcinoid	7	4.2	
Mixed cancer types	12	7.1	
Neuroendocrine cancer	7	4.2	
NSCLC of null immunophenotype	7	4.2	
Squamous-cell carcinoma	49	29.2	
Total	168	100.0%	

A Pearson Chi Square test;*significance level p<0.05

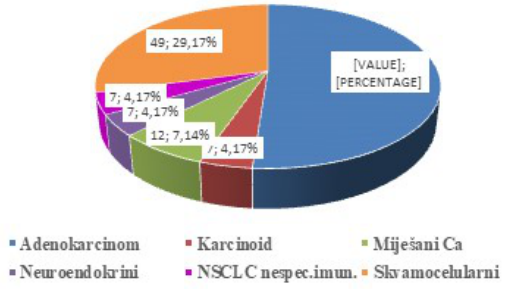

Figure 2 **Distribution of lung cancer types in patients who underwent lung resection up to the level of lobectomy (n=168).**

Adenocarcinoma, observed in 86 patients (51.2%), was the most frequent histopathological diagnosis among patients with NSCLC, showing a statistically significant difference between observed and expected frequencies ($p<0.001$) (Table 2 and Figure 2).

Table 3 **Univariate analysis of the association between neoadjuvant therapy and PAL (>6 days, PAL+) in patients with NSCLC who underwent lung resection up to the level of lobectomy (n=168).**

Variable	PAL+ (Air leak >6 days) (n=64)	PAL- (Air leak ≤6 days) (n=104)	Total (n=168)	RR 95% CI	p-value
Neoadjuvant therapy					
No	59 (37.6%)	98 (62.4%)	157 (93.5%)	1.00	[a]0.750
Yes	5 (46.5%)	6 (54.5%)	11 (6.5%)	1.21 (0.614 - 2.383)	

PAL (engl. Prolonged Air Leak); RR 95%CI - relative risk 95% Confisence Interval aFisher¨s Exact test; significance level p<0.05

In 11 (6.5%) participants, neoadjuvant therapy was administered. The association between the use of neoadjuvant therapy and the development of PAL was not significant, as the observed frequencies did not differ statistically from the expected ones ($p=0.750$). In the group of participants who received neoadjuvant therapy, out of a total of 11 participants, air leak>6 days (PAL+) developed in 5 (46.5%), which is 1.21 times more than in participants who did not receive neoadjuvant therapy. However, the calculated 95% confidence interval for the relationship between PAL occurrence and the use of neoadjuvant therapy indicates no association, RR=1.21, 95% CI (0.614–2.383) (Table 3).

Table 4 **Univariate analysis of the association between the histopathological diagnosis and PAL (>6 days, PAL+) in patients diagnosed with NSCLC who underwent pulmonary resection up to the level of lobectomy (n=168).**

Variable	PAL+ (Air leak >6 days) (n=64)	PAL- (Air leak ≤6 days) (n=104)	Total (n=168)	RR 95% CI
Histopathological diagnosis				
Adenocarcinoma	33 (38.4%)	53 (61.6%)	86 (51.2%)	[a]0.968
Squamous-cell carcinoma	18 (36.7%)	31 (63.3%)	49 (29.2%)	
Other	13 (39.4%)	20 (60.6%)	33 (19.6%)	
Total	64 (38.1%)	104 (61.9%)	168 (100.0%)	

PAL (engl. Prolonged Air Leak); RR 95%CI - relative risk 95% Confisence Interval aFisher¨s Exact test; significance level p<0.05

In more than half of the participants, adenocarcinoma was confirmed histopathlogically, 86 (51.2%). The association between the histopathological diagnosis and the development of PAL was not significant, as the observed frequencies did not differ statistically from the expected ones (p=0.968) (Table 4).

DISCUSSION

As in most comparative studies, this study also aimed to determine whether an association between the administration of neoadjuvant therapy and PAL>6 days exists and, if so, to which extent. Among the participants included in this study, 11 (6.5%) received neoadjuvant therapy prior to surgery, of whom 5 (46.5%) developed PAL. Among participants who did not receive neoadjuvant therapy, 157 (93.5%), a total of 59 (37.6%) developed PAL. Therefore, when considering these two variables, no statistical association was demonstrated between the expected and observed frequencies; in other words, the administration of neoadjuvant therapy and PAL were not dependent (p=0.750), with the caveat that the sample size was insufficient for a precise and valid conclusion.

Patients who were classified as borderline operable, inoperable, or unresectable following diagnostic evaluation became candidates for neoadjuvant therapy according to the oncological protocol. After neoadjuvant therapy, diagnostic reevaluation was performed, including a new chest CECT scan and bronchoscopy. Based on the degree of achieved tumor regression, patients were reconsidered candidates for surgical intervention. The extent of resection was determined by the degree of regression, and the majority of such patients ultimately required resections greater in extent than lobectomy, such as bilobectomy and most commonly pneumonectomy, and were therefore excluded from the study. There were also cases in which surgery resulted only in exploration, and these patients were likewise excluded. For this reason, only a small number of such patients were included in the study.

Postoperative follow-up in this study showed that neoadjuvant therapy, in our sample, did not have a significant impact on the occurrence of PAL. This statement may be accepted if neoadjuvant therapy is considered as an isolated potential risk factor. Its catalytic role in combination with other risk factors for PAL remains a subject open to further discussion. These findings are consistent with results available in the relevant literature on this topic (7-12). The absence of an effect of neoadjuvant therapy on PAL is also supported by findings from studies by other authors. Lyang S, Ivanović J, Gilbert S, et al., are among those who reported a non-significant association between the administration of neoadjuvant therapy and PAL>6 days.

CONCLUSION

Neoadjuvant therapy, as an isolated factor, does not have a significant impact on the occurrence of PAL.

REFERENCES

1. Drewbrook C, Das S, Mousadoust D, Nasir B, Tayebi S, Firouzbakht K, et al. Incidence risk and independent predictors of prolonged air leak in 269 consecutive pulmonary resection patients over nine months: a single-center retrospective cohort study. Open J Thorac Surg. 2016;6(4):33-46. doi: 10.4236/ojts.2016.64006
2. Goto M, Aokage K, Sekihara K, Miyoshi T, Tane K, Yokoi K, et al. Prediction of prolonged air leak after lung resection using continuous log data of flow by digital drainage system. Gen Thorac Cardiovasc Surg. 2019;67(8):684-9. doi: 10.1007/s11748-019-01073-y
3. Liang S, Ivanovic J, Gilbert S, Maziak DE, Shamji FM, Sundaresan RS, et al. Quantifying the incidence and impact of postoperative prolonged alveolar air leak after pulmonary resection. J Thorac Cardiovasc Surg. 2013;145(4):948-54. doi: 10.1016/j.jtcvs.2012.08.044
4. Burt BM, Shrager JB. Prevention and management of postoperative air leaks. Ann Cardiothorac Surg. 2014;3(2):216-8. doi: 10.3978/j.issn.2225-319X.2014.02.12
5. Brunelli A, Monteverde M, Borri A, Salati M, Marasco RD, Fianchini A. Predictors of prolonged air leak after pulmonary lobectomy. Ann Thorac Surg. 2004;77(4):1205-10. doi: 10.1016/j.athoracsur.2003.10.082
6. Brunelli A, Varela G, Refai M, Jimenez MF, Pompili C, Sabbatini A, et al. A scoring system to predict the risk of prolonged air leak after lobectomy. Ann Thorac Surg. 2010;90(1):204-9. doi: 10.1016/j.athoracsur.2010.02.054
7. Pompili C, Miserocchi G. Air leak after lung resection: pathophysiology and patients' implications. J Thorac Dis. 2016;8(Suppl 1):S46-S54. doi: 10.21037/jtd.2016.02.16
8. Venuta F, Rendina EA, De Giacomo T, Flaishman I, Guarino E, Ciccone AM, et al. Technique to reduce air leaks after pulmonary lobectomy. Eur J Cardio-Thoracic Surg. 1998;13(4):361-4. doi: 10.1016/S1010-7940(98)00101-0
9. Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. Chest. 2002;122(3):1037-57. doi: 10.1378/chest.122.3.1037
10. Stolz AJ, Schützner J, Lischke R, Simonek J, Pafko P. Predictors of prolonged air leak following pulmonary lobectomy. Eur J Cardio-Thoracic Surg. 2005;27(2):334-6. doi: 10.1016/j.ejcts.2004.11.004
11. Mueller MR, Marzluf BA. The anticipation and management of air leaks and residual spaces post lung resection. J Thorac Dis. 2014;6(3):271-84. doi: 10.3978/j.issn.2072-1439.2013.11.29
12. Pan H, Chang R, Zhou Y, Gao Y, Cheng Y, Zhang C, et al. Risk factors associated with prolonged air leak after video-assisted thoracic surgery pulmonary resection: a predictive model and meta-analysis. Ann Transl Med. 2019;7(5):103. doi: 10.21037/atm.2019.02.17

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Inflamatory Response after Veins Sclerotherapy with Sodium Tetradecyl Sulfate

Inflamatorni odgovor nakon sklerozacije vena sa natrijum tetradecil sulfatom

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ABSTRACT

Introduction: to measure inflamatory response after Ultrasound guided foam sclerotherapy (UGFS) of varicose vein with sodium tetradecyl sulfate (STS). All inflamatory parameters vere mesaured and compared right after treatment and 7 days after treatment. Aim: to measure inflamatory response after Ultrasound guided foam sclerotherapy (UGFS) of varicose vein with sodium tetradecyl sulfate (STS). Materials and methods: the following parameters were measured: C-reactive protein, D-dimer, fibrinogen and leukocytes. We included 41 patients with indications for treatment of vein sclerotherapy. Total of 82 samples were taken from cubital vein, right after treatment and 7 days after treatment. Results: the values of only one parameter were different. A significant difference in the measurement immediately after the treatment and seven days after the treatment, was in the value of d-dimer. Significant increases of D-dimer values was seven days after treatment. D-dimer level increased from an average 322.1 to 446.9, which we found to be statisticaly significant with a p value of <0,001. No difference were found for other parameters. Conclusion: in our study, D-dimers were shown to be a specific inflammatory parameter, unlike others, in the treatment of veins sclerotherapy, with sodium tetradecyl sulfate. The increase in D-dimer values did not affect blood hypercoagulability. Sclerosis of varicose veins with sodium tetradecyl sulfate proved to be an extremely effective, safe and reliable treatment.

Keywords: D-dimer, labaratory, sclerosation, varicose veins

SAŽETAK

Uvod: je bio izmjeriti upalni odgovor nakon ultrazvučno vođene skleroterapije pjenom (UGFS) proširenih vena natrijum tetradecil sulfatom (STS). Svi upalni parametri su izmjereni i upoređeni odmah nakon tretmana i 7 dana nakon tretmana. Cilj: izmjeriti upalni odgovor nakon sklerozacija vena pjenom pod kontrolom ultrazvuka (UGFS) natrijevim tetradecil sulfatom (STS). Materijali i metode: sljedeći parametri su izmjereni: C-reaktivni protein, D-dimer, fibrinogen i leukociti. Uključili smo 41 pacijenta s indikacijama za liječenje skleroterapijom vena. Ukupno 82 uzorka uzeto je iz kubitalne vene, odmah nakon tretmana i 7 dana nakon tretmana. Rezultati: vrijednosti samo jednog parametra su se razlikovale. Značajna razlika u mjerenju odmah nakon tretmana i sedam dana nakon tretmana bila je u vrijednosti D-dimera. Značajno povećanje vrijednosti D-dimera bilo je sedam dana nakon tretmana. Nivo D-dimera se povećao sa prosječnih 322,1 na 446,9, što smo utvrdili kao statistički značajno sa p vrijednošću <0,001. Za ostale parametre nije pronađena razlika. Zaključak: u našoj studiji, D-dimeri su se pokazali kao specifični inflamatorni parametar, za razliku od drugih, u liječenju skleroterapije vena natrijum tetradecil sulfatom. Povećanje vrijednosti D-dimera nije uticalo na hiperkoagulabilnost krvi. Skleroza proširenih vena natrijum tetradecil sulfatom pokazala se kao izuzetno efikasan, siguran i pouzdan tretman.

Ključne riječi: D-dimer, laboratorija, sklerozacija, proširene vene

INTRODUCTION

Veins have been mentioned since the time of Hippocrates (1). Vein surgeries have their own history. After the first descriptions of varicose veins, attempts to solve them also began. We will focus in particular on phlebectomy and perforator vein surgery and with minimally invasive methods (1).

The veins of the legs become dilated and blue color due to excessive accumulation of blood. This disease and the effort to identify and treat it have a very long history (2).

In his publication, Orbach listed the type of sclerosing agent used in sclerotherapy and mentioned a new synthetic surfactant - sodium tetradecyl sulfate (STS) (3).

The breakthrough in the treatment of this method was due to the development of sodium tetradecyl sulfate STS (sodium tetradecyl sulfate) in 1946 and its use by the German surgeon Leopold Reiner. This drug proved to be much more effective and at the same time with minimal complications (4,5). In the 1960s, the Irishman George Fegan introduced modern compression sclerotherapy in the Lancet (1963), and re-popularized this method. In an article entitled "Continuous Compression Technique After Treatment of Varicose Veins", he described a study in which over 13,000 patients participated. He treated varicose veins by injecting 0.5ml, 3% STS and gave 10-20 injections in one session (6,7)

The mechanism of sclerotherapy is the destruction of the venous endothelium of the blood vessel. When the basal layer is affected by a sclerosing agent, vasospasm is induced, and then completes fibrosis of the blood vessels. Sclerosants enter the deep venous system through perforators, but the risk of deep vein thrombosis or pulmonary embolism after sclerotherapy is very low. (8,9)

The use of foam sclerosing agents has been shown to be more effective and reliable than liquid sclerosing agents. It works at lower concentrations than liquid sclerosing agents. The use of foam reduces the amount of drug required, improves the sclerosing effect by increasing the contact surface with the walls of varicose veins, and prevents intravascular bleeding (10). It has been repeatedly demonstrated that foam sclerosing therapy has a success rate of 85-95% compared to 35% for liquid in eliminating reflux in large cutaneous veins. Also, histological studies have shown similar effects of sclerosing agents at concentrations of 0.5% as foam and 3% as a liquid (11).

In the last 15 years, vein sclerotherapy has experienced a great expansion, although its use began much earlier. Our experience dates back 15 years and over 3000 treatments have been recorded (12).

There are studies that have verified laboratory parameters after sclerotherapy as well as the occurrence of blood hypercoagulability (13,14). However, no specific studies have been found that compare and measure laboratory parameters such as D-dimers, fibrinogen and platelets. In this study, the aim was to investigate specific inflammatory parameters that could be specific to this type of treatment and which would be useful in future practice.

AIM

The aim of the study was to measure inflamatory response after Ultrasound guided foam sclerotherapy (UGFS) of varicose vein with sodium tetradecyl sulfate (STS).

MATERIALS AND METHODS

Patients and study design

The study included the total of 41 (82 samples). It was designed as a prospective, observational, interventional clinically controlled study. The study was conducted at the Cantonal Hospital Zenica and competent laboratories. The study included patients who underwent minimally invasive treatment of varicose veins by ultrasound guided foam sclerotherapy (UGFS) during the period of 14 months.

The inclusion criteria were: patients older than 18 and younger than 65 years of age, patients with clinically and ultrasound-verified varicose veins of the lower extremities, disease stage from Ido IV according to the Clinical, Etiological, Anatomical and Pathophysiological (CEAP) classification (4). Exclusion criteria were patients younger than 18 and older than 65, disease stage according to CEAP classification 0,V and VI, previous deep vein thrombosis and pulmonary thromboembolism, chronic diseases: myocardial infarction, degenerative diseases of blood vessels, patients who did not consent to participate in the trial, patients who independently stopped the research, patients who did not have all the planned parameters taken, peripheral arterial ischemia, pregnancy, disability. In stageV and VI of varicose veins patients were excluded because the disease is developed and advanced with additional complications such as venous ulcers, which can affect the values of the measured parameters being tested. Also, chronic venous thrombosis and thromboembolic incidents often give false positive laboratory values, and such patients were excluded from the study.

Each patient gave written consent for the study and was informed in detail about all protocols and procedures of this study. Patients under the age of 18 could not give their consent, and according to the pathophysiology of venous diseases, they could not be part of this study. Patients older than 65 are often burdened with additional comorbidities, which could affect the results of the study.

The study was approved by the Ethics Committee of the Cantonal Hospital Zenica.

All patients included in study, had a minimum of two visits to a doctor, initial and control treatment, and two visits to the laboratory. The first visit was during the procedure and vein treatment itself, then they were referred to the laboratory, and the same procedure was repeated after 7-10 days. The study lasted fourteen months.

After the physical examination, each patient underwent an ultrasound (Color Doppler) examination of the blood vessels of the lower extremities (Biosound esoate MyLab 25 Xvision probe 5-10Hz, Genoa/ Italy). The examination of the arterial and deep venous system was performed in the supine position, while the superficial venous system was performed in the standing position. The measurements were done for the sufficiency of the saphenous-femoral junction, and the sufficiency of small saphenous vein.

Immediately before the treatment, patients were administered low-molecular-weight heparin in a dose determined according to body weight (15). Sclerotherapy was performed in a standing, sitting and lying position.

After the preparation, the treatment protocol for each patient was standardized. The sclerosant Sodium tetradecyl sulfate (Fibrovein®, manufacturer STD Pharmaceutical Product LTD Hereford, England) was used. Sclerosing foam was obtained using a sterile disposable syringe set (20 mL two-piece, thre-waystopCock syringe connector). The mixture of sclerosing fluid and room air was 1+4 (one volume of sclerosing agent + four volumes of air; i.e., a ratio of 1/5). Foam preparation and venipuncture were performed according to the Tessari method (16).

Sclerotherapy was guided by ultrasound and performed by direct needle puncture (22 Gauge, length 40 mm, Terumo® Leuven; Belgium), with the patient in the supine and standing positions. The sclerosing agent was applied as a foam. Immediately after the treatment for 10-15 minutes, the patient had blood drawn from the cubital vein by venipuncture for analysis of laboratory findings, as follows: complete blood count (CBC) – leukocytes (reference value 4-10x109/L) (Sysmex xn-350, Kobe/Japan), C reactive protein (CRP) (reference value<5 mg/dL) (Olympus AU400, Nagano/Japan), Fibrinogen (reference value 1.9-4.3 g/L) (Stago Gennevilliers/France), D-dimer (reference value 50-500 ng/mL) (Afias 1, Gangneung/South Korea).

A follow-up examination and monitoring was performed 7-10 days after the treatment. At that time, a new reevaluation and examination of the patient was performed. For a more detailed analysis, the patients were statistically processed and divided according to the concentration of the sclerosing agent with which they were treated. The patients were treated with five different concentrations of Sodium tetradecyl sulfate: four patients with 1%, six with 1.5%, 20 with 2%, seven with 2.5% and four patients with 3% polidicanol.

Statistical analysis

Numerical variables were presented as arithmetic means and standard deviations (SD), and as medians, interquartile ranges (IR Q1–Q3), and ranges (min-max) if they did not follow a normal distribution. Quantitative variables were tested for normality using the Shapiro-Wilk test and evaluated with QQ-plots and histograms. Ordinal and categorical variables were described using medians and interquartile ranges, or, as discrete values, presented with frequency distributions. For dependent measurements, a paired t-test was applied if the assumptions for its use were met. The statistical significance level was set at <0.05. We presented results in tables and graphs, and stated which p values and which hypothesis test were used. 95% confidence interval was used in the results.

RESULTS

Among 41 patients, 14 (34%) were male and 27 (66%) were female. The mean age of the patients in the total sample was 42±13 years. The median age was 42 years (IR= 32 and 49) years.

Analysis of inflammatory markers in the patients treatet with Sodium tetradecyl sulfate between the time points immediately after treatment and seven days after treatment showed the difference. The most prominent findings were the significant changes in D-dimer level, which showed significant increase 7 days after treatment. Mean value of D-dimer levels increased from 322.1 ng/mL to 446.9 ng/mL (p=0.04) (Table I and Figure 1).

We performed a more detailed statistical analysis of different concentrations of Sodium tetradecyl sulfate in order to check whether a particular concentration of Sodium tetradecyl sulfate had a significant effect on the results. The results showed no statistically significant difference in D-dimer values according to different concentrations of sclerosing agents (Figure 2).

Concentration of other markers, including C-reactive protein (CRP), fibrinogen, and leukocytes, did not show statistically significant differences during this post-operative period. CRP level showed a slight increase from an average of 1.9 mg/dL to 2.3 mg/dL. Similarly, fibrinogen level increased slightly from an average of 3.5 g/L to 3.9 g/L, leukocytes increased from 6.3 x 109/L to 6.6 x 109/L (Table I).

There was no statistically significant difference in CRP values right after treatment and seven days after treatment. The mean value increased by -0.40 (±2.4) mg/dL (Table I).

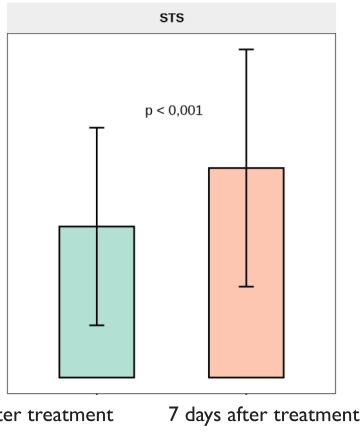

Figure 1 **D-dimer values after treatment and 7 days after treatment.**

Table 1 **Values of laboratory measurements immediately after the treatment and 7 days after the treatment.**

Variable(reference value)	Sample timing				
	After the treatment	7 days after the treatment	Difference*	95% CI*,†	P*
C-reactive protein (<5) (mg/dL)			0.40	-1.1; 0.35	0.3
Mean (±SD)	1.9 (±2.4)	2.3 (±2.7)			
Median (Q 1–Q3)	1.1 (0.6–1.7)	1.6 (0.8–2.6)			
Range (Min–Max)	0.4–9.1	0.5–16.5			
D-dimer (50-500) (ng/mL)			-125	-187; -63	<0.001
Mean (±SD)	322.1 (±210.8)	446.9 (±253.0)			
Median (Q1–Q3)	311.3 (179.0–354.0)	423.0 (234.0–622.3)			
Range (Min–Max)	33.0–1340.0	134.0–1226.0			
Fibrinogen (1.9-4.3) (g/L)			-0.19	-0.44; 0.07	0.2
Mean (±SD)	3.5 (±0.6)	3.7 (±0.8)			
Median (Q1–Q3)	3.5 (3.1–3.8)	3.9 (3.3–4.3)			
Range (Min–Max)	2.1–4.8	2.1–4.8			
Leukocytes (4-10) (10^9/L)			-0.25	-0.70; 0.19	0.3
Mean (±SD)	6.3 (±1.1)	6.6 (±1.5)			
Median (Q1–Q3)	6.3 (5.6–6.9)	6.5 (5.7–7.5)			
Range (Min–Max)	3.8–8.7	3.0–9.9			

*refers to the Difference, p and 95% CI (Confidence interval) columns;
† indicates the 95% CI that refers to where the two are in the table

No statistically significant difference was found in fibrinogen values after treatment and 7 days after treatment. The average value increased by 0.19 (±0.8) g/L. No statistically significant difference was found in leukocytes values after treatment and 7 days after treatment. The average value increased by 0.25 (±1.4) × 109/L (Table 1).

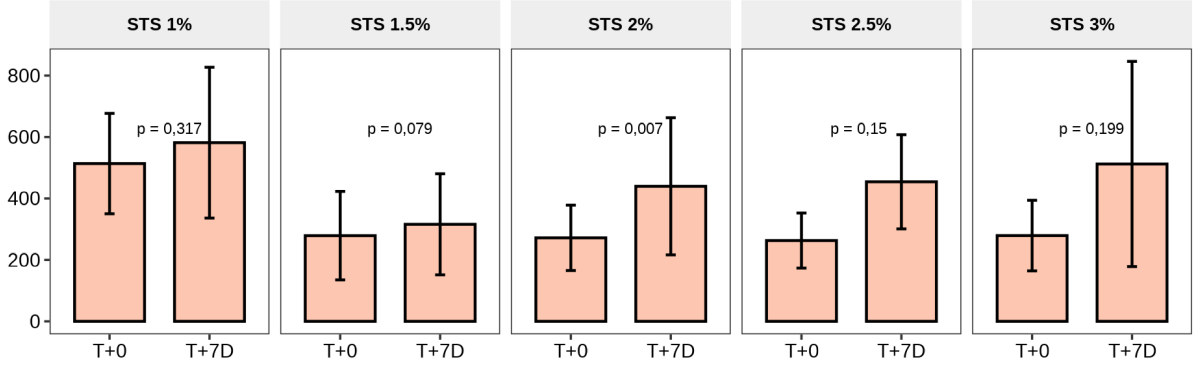

Figure 2 **D-dimer values immediately after and 7 days after treatment, according to different concentrations of sclerosing agents.**

DISCUSSION

Nowdays, there are a large number of non-invasive methods of varicose vein treatment that have proven to be very effective and reliable (17). Today, detergent-based sclerosing agents have gained the greatest popularity. Polidocanol (lauromacragol) and sodium tetradecyl sulfate are the two sclerosing agents that are most common and most widely used due to their effectiveness, non-toxicity, and affordable price (18).

Patients, that we treated with Sodium tetradecyl sulfate, biohumoral response showed difference. Difference noted right after treatment and seven days after treatment.

The most significant changes were in D-dimer, where measurements after seven days were significantly increased after usage of Sodium tetradecyl sulfate. Our results are in line with a large number of other studies that have confirmed the elevation of D-dimer levels after sclerotherapy with sodium tetradecyl sulfate (STS) (19,20).

The D-dimer values showed a significant difference in measurements immediately after treatment and seven days after treatment in patients treated with Sodium tetradecyl sulfate. Previous results and research related to D-dimers have also undoubtedly confirmed that differences in different measurements exist, mostly due to the procoagulant activity that occurs; however, this difference is still insufficient to cause harmful consequences or disrupt the general condition of the coagulant system and events during and after treatment of the venous system (21).

C-reactive protein CRP and fibrinogen are acute phase proteins that increase as nonspecific inflammatory markers. In the literature, elevated values of D-dimer and CRP parameters can be found in patients with varicose veins and some other comorbidities, such as hypertension (22). Since these parameters are nonspecific, it is very difficult to analyze and isolate their response to an exact and specific change occurring in the body. The reason for the increase in values may be a damaged wall and destroyed endothelium, which enhance procoagulant activity in the blood, and thus activate processes that increase the value of the aforementioned parameters (17,23) Recent research shows that CRP values are slightly elevated in patients with varicose veins and in patients who have undergone minimally invasive treatments. Changes are minimal and negligible in medical practice (23).

C reactive protein was not statistically significant nor showed a statistically significant difference immediately after treatment and seven days after treatment. It is interesting that the average value after 7 days was lower. Reportedly, no significant difference in CRP levels immediately and 7 days after Sodium tetradecyl sulfate treatment was found (24,25).

Fibrinogen levels were slightly changed but without statistically significant difference after treatment and seven days later. Fibrinogen is one of the main parameters in the procoagulant activity of blood and its values can be changed under the influence of various parameters. Even varicose veins themselves can cause an elevation of blood fibrinogen level (27). Changes in fibrinogen level in our study were minimal. A large number of studies also showed minimal non-significant differences in fibrinogen levels (26,27).

The results of the analysis of formed blood elements were without significant difference in values. Most similar studies state that sclerosing agents do not have a significant effect on formed blood elements (28,29).

Limtation of this study was relatively small number of patients and samples, but still enough for moderate statistical power, and the study was conducted in a single center. Also, obtained data after firts follow up for some patients were inssufitient. Majority of patiend had one month and three month follow up. We din't show all clinical outcome and stratification of patients because they did not have impact on the results.

CONCLUSION

Sodium tetradecyl sulfate is a safe sclerosant and does not cause severe complications such as thromboembolic effects nor does it provide a biohumoral response related to the onset of thrombotic incidents. Chosing an adequate sclerosant is related to the diameter of the vein. The minimum concetration of sclerosant, required to achieve total endothelial dysfunction, is 0.5%. The sclerosing agents are effective for 7 days after treatment, so recovery should be adjusted to this knowledge (compression therapy, repeated treatment, etc.). For maximum effect and good effect, it is important that the patient is adequately prepared, the choice of the treated vein, the choice of concentration, adequate monitoring of the patient and control with diagnostic and laboratory tests. Foam vein sclerotherapy is an extremely effective and reliable method of treating varicose veins, and its use will have even wider application in the future.

REFERENCES

1. Van den Bremer J, Moll FL. Historical overview of varicose vein surgery. Ann Vasc Surg. 2010;24:426-32. doi:10.1016/j.avsg.2009.07.035
2. Asadi MH, Van Hee R, Khosravi A, Shojaee R, Changizi-Ashtiyani S, Amini S. The historical course of varicose vein surgery in the Persian medicine. Acta Chir Belg. 2023; 123:589-600. doi:10.1080/00015458.2023.2254603
3. Myers K. A history of injection treatments - II sclerotherapy. Phlebology 2019;34:303-10. doi:10.1177/0268355518798283
4. Whiteley MS, Smith VC. Exacerbation of alopecia areata: A possible complication of sodium tetradecyl sulphate foam sclerotherapy treatment for varicose veins. SAGE Open Med Case Rep. 2017; 5:205. doi:10.1177/2050313X17712643
5. Baldazzi G, Tessari M, Zamboni M, Pagani A, Zamboni P. The sex prevalence of lower limb varicose vein networks. J Vasc Surg Venous Lymphat Disord 2024; 12:101944. doi:10.1016/j.jvsv.2024.101944
6. Gibson K, Gunderson K. Liquid and Foam Sclerotherapy for Spider and Varicose Veins. Surg Clin North Am. 2018; 98:415-29. doi:10.1016/j.suc.2017.11.010
7. Liu JW, Ni B, Gao XX, Bin H, Qiang-Qiang N, Xue Qiang F et al. Comparison of bleomycin polidocanol foam vs electrochemotherapy combined with polidocanol foam for treatment of venous malformations J Vasc Surg Venous Lymphat Disord. 2024; 12:101697. doi:10.1016/j.jvsv.2023.101697
8. Davies HO, Watkins M, Oliver R, Berhane S, Bradbury AW. Adverse neurological events after sodium tetradecyl sulfate foam sclerotherapy - A prospective, observational study of 8056 treatments. Phlebology 2022;37:97-10. doi:10.1177/02683555211051490
9. Becker GH, Holden RW, Heun YY, Klatte EC. Ablation with absolute alcohol. Interv Radiol. Baltimore:Williams and Wilkins. 1992: 135-52. doi: 10.1001/jama.2020.16195
10. Schmitt N, Lorenz J, Hohenstatt S, Semmelmayer K, Ruping F, Hoffmann J, et al. Sclerotherapy of Venous Malformations Using Polidocanol: Effectiveness, Safety, and Predictors of Outcomes and Adverse Events. J Vasc Interv Radiol. 2023;34:2103-9. doi:10.1016/j.jvir.2023.08.032
11. de Ávila Oliveira R, Riera R, Vasconcelos V, Baptista-Silva JC. Injection sclerotherapy for varicose veins. Cochrane Database Syst Rev 2021; 12:1732. doi:10.1002/14651858.CD001732.pub3
12. Lim C, Lee S, Ghosh A, Funaki B. Embolic Agents: Sclerotherapy. Semin Intervent Radiol. 2024;41(1):79-83. doi:10.1055/s-0043-1778656.
13. Mangiafico M, Costanzo L. Superficial Venous Thrombosis: A Comprehensive Review. Healthcare. 2024;12(4):500. doi:10.3390/healthcare12040500
14. Connor DE, Joseph JE, Exner T, Ma DD, Parsi K. Infusion of foam sclerosants results in a distance-dependent procoagulant activity, haemoconcentration and elevation of D-dimer levels. Phlebology. 2014; 29(10):677-87. doi:10.1177/0268355513502333
15. Gigante B, Tamargo J, Agewall S, Atar D, Ten Berg J, Campo G, et al. Update on antithrombotic therapy and body mass: a clinical consensus statement of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and the European Society of Cardiology Working Group on Thrombosis. Eur Heart J Cardiovasc Pharmacother. 2024; 10(7):614-45. doi:10.1093/ehjcvp/pvae064
16. Azmoun S, Liu Y, Bian K, Chen A, Liu S. The Effect of Pushing Rate on Foam Stability in the Tessari Method. Dermatol Surg. 2024;50(6):542-5. doi: 10.1097/DSS.0000000000004155 Mol Cell Cardiol. 2022;168:58-67. doi:10.1016/j.yjmcc.2022.04.011

17. Nappi F, Fiore A, Masiglat J, Cavuoti T, Romandini M, Nappi P, et al. Endothelium-Derived Relaxing Factors and Endothelial Function: A Systematic Review. Biomedicines. 2022;10(11):2884. doi: 10.3390/biomedicines10112884
18. Arasakumar DRB, Pang C, Evans N, Papadopoulou A, Khalifa, Tsui J et al. Efficacy and safety of foam sclerotherapy with sodium tetradecyl sulfate as preferred sclerosant of venous malformations based on experience from a single specialist center. J Vasc Surg Venous Lymphat Disord. 2023;11(2):379-88. doi: 10.1016/j.jvsv.2022.10.008
19. Patel KP, Patel NB, Patel SA, Patel HB. Comparison of Blood Biomarkers in Systemic Blood and Varicose Veins: A Cross-sectional Study J Clin of Diagn Res. 2024;18(4):01-05. doi: 10.7860/JCDR/2024/67598.19227.
20. Zhao F, Wang D, Kang N, Hai Y. Changes of D-dimer level after lumbar fusion surgery and its role in predicting deep venous thrombosis. Inter J of Surg. 2024;62(5):612-6. doi: 10.1097/IO9.0000000000000178
21. Jabs WJ, Theissing E, Nitschke M, Bechtel JF, Duchrow M, Mohamed S, et al. Localgenerationof C-reactive protein in diseased coronary artery venous bypass grafts and normal vascular tissue. Circulation. 2003;108(12):1428-31. doi: 10.1161/01.CIR.0000092184.43176.91
22. Skuła M, Hobot J, Czaja J, Simka M. The effect of the calibre and length of needle on the stability of sclerosing foam. Phlebology. 2021;36(4):322-8. doi: 10.1177/0268355520953317
23. Czeczelewski M, Mikos E, Moqbil S, Szmygin M, Szmygin H, Pyra K. Concentration of Inflammatory Markers in Plasma of Varicose Ovarian Veins in Women With Pelvic Venous Disorders: A Pilot Study. Eur J Vasc Endovasc Surg. 2023;66(4):597-8. doi: 10.1016/j.ejvs.2023.06.011
24. Turan HT, Meuwly M. Spectroscopy, Dynamics, and Hydration of S-Nitrosylated Myoglobin. J Phys Chem B. 2021;125(17):4262-73. doi: 10.1021/acs.jpcb.0c10353
25. Uhl J-F, Gillot C. Anatomy of Perforating veins of the lower limb. Phlebology. 2012;27(5):219-30. doi: 10.1258/phleb.2012.012b01
26. Gwozdzinski L, Pieniazek A, Gwozdzinski K. Factors Influencing Venous Remodeling in the Development of Varicose Veins of the Lower Limbs. Int J Mol Sci. 2024;25(3):1560. doi: 10.3390/ijms25031560
27. Saberianpour S, Modaghegh MHS, Rahimi H, Kamyar MM. Role of mechanosignaling on pathology of varicose vein. Biophys Rev. 2021;13(1):139-45. doi: 10.1007/s12551-021-00783-z
28. Gawas M, Bains A, Janghu S, Kamat P, Chawla P.A Comprehensive Review on Varicose Veins: Preventive Measures and Different Treatments. J Am Nutr Assoc. 2022;41(15):499-510. doi: 10.1080/07315724.2021.1909510
29. Wang L, Cheng CK, Yi M, Lui KO, Huang Y. Targeting endothelial dysfunction and inflammation.J

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Angiogenesis in Renal Cell Carcinoma: Correlation with Pathohistological Features of the Tumor and its Prognostic Significance

Angiogeneza kod karcinoma bubrežnih stanica: korelacija sa patohistološkim osobinama tumora i prognostički značaj

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ABSTRACT

Introduction: angiogenesis is the basis of tumor growth and metastasis. The microvessel density is the number of blood vessels per unit area and it is the most frequently used parameter to quantify intratumoral angiogenesis. Aim: to determine the relationship between angiogenesis and various histopathologic features in renal cell carcinoma and also to evaluate the prognostic significance of angiogenesis. Materials and methods: microvessel density was quantified by using immunocytochemical staining of endothelial cells with endoglin (CD105) - related antigen in 120 tumor specimens. Samples were obtained from patients who underwent nephrectomy at the Urology Clinic, Clinical Center University of Sarajevo. Results: tumor angiogenesis was highest in clear cell renal cell carcinoma.The nonparametric Kruskal-Wallis test confirmed a significant difference between renal cell carcinoma subtypes p=0.000475, (p<0.001). Angiogenesis increased in correlation with higher TNM stages of renal cell carcinoma. Using a parametric One-Way ANOVA test, strong evidence was found for differences in mean MVD-CD105 values across TNM stages of renal cell carcinoma, F(3.116)=3.938, p=0.010. No correlation was observed with other pathohistological characteristics of renal cell carcinoma. At the end of the five- year follow-up, the average survival for the high-angiogenesis group was 54.75 months (95% CI [50.56–58.94]), which was longer than the survival period for patients with low or moderate angiogenesis. Conclusion: although results indicated that angiogenesis was greater in clear cell carcinoma and higher TNM stage - parameters typically associated with a poorer prognosis, this study shows that subjects with higher angiogenesis had a higher survival rate at the end of each year during the five-year follow-up compared to those with low or moderate angiogenesis.

Keywords: renal cell carcinoma, angiogenesis, the microvessel density, CD105

SAŽETAK

Uvod: angiogeneza je osnova tumorskog rasta i metastaziranja. Parametar koji se najčešće koristi za kvantifikaciju intratumorske angiogeneze je gustina mikrovaskularnih elemenata, odnosno broj krvnih žila po jedinici površine. Cilj: odrediti odnos između angiogeneze i različitih histopatoloških osobina tumora bubrežnih stanica te odrediti prognostički značaj angiogeneze. Materijal i metode: gustoća mikrovaskularnih elemenata je kvantificirana sa imunohistohemisjkim bojenjem endotelijalnih stanica sa antitjelom na endoglin (CD105) na 120 uzoraka tumora bubrežnih stanica uzetih od pacijentata podvrgnutih nefrektomiji. Svi pacijenti su hospitalizirani i operisani na Urološkoj klinici KCUS. Rezultati: tumorska angiogeneza je najveća kod svijetlostaničnog karcinoma bubrega. Primjenom neparametrijskog Kruskal-Wallis testa potvrđeno je postojanju razlike između različitih podtipova karcinoma bubrežnih stanica p=0,000475 (p<0,001). U odnosu na TNM stadij karcinoma bubrežnih stanica, angiogenza je veća kod višeg stadija. Primjenom parametrijskog One-Way ANOVA testa dobiven je snažan dokaz o postojanju razlike između prosječnih vrijednosti MVD-CD105 kod TNM stadija renalnog karcinom, F(3,116)=3,938, p=0,010. Sa ostalim patohistološkim karakteristikama karcinoma bubrežnih stanica nije uočena korelacija. Na kraju pete godine praćenja prosječno preživljavanje u grupi ispitanika sa većom angiogenezom je 54,75 mjeseci, 95%CI [50,560-58,940] što je duže u odnosu na preživljavanje pacijenata sa niskom ili umjerenom angiogenezom. Zaključak: iako su rezultati ukazali da je angiogeneza veća kod svijetlostaničnig karcinoma i većeg TNM stadija, a to su parametri koji ukazuju na lošiju prognozu, istraživanje pokazuje da su ispitanici sa izraženom angiogenezom imali višu proporciju preživljavanja na kraju svake godine tokom pet godina praćenja u odnosu na ispitanike sa niskom i umjerenom angiogenezom.

Ključne riječi: karcinom bubrežnih stanica, angiogeneza, gustina mikrovaskularnih elemenata, Cd105

INTRODUCTION

Angiogenesis is the basis of tumor growth and metastasis. Greenblatt and Shubik were the first to describe angiogenesis as a driver of tumor growth in 1968, followed by Folkman J in 1971 (1). Given that oxygen diffusion in tissue is limited to approximately 100 Ꮅm (2), angiogenesis becomes necessary for further growth once a tumor reaches a size of 1-2 mm (roughly 106cells). Tumor blood vessels are characterized by thin walls, a tortuous appearance, a localized lack of pericytes, and irregular vessel diameters. The initiation of the angiogenic process within a tumor is associated with changes in the local balance between proangiogenic and antiangiogenic regulators (3). Changes in the balance are caused by hypoxia, low pH, hypoglycemia, mechanical pressure, inflammatory response and genetic mutations. Just as a tumor's angiogenic potential is determined by oncogenes and tumor suppressor genes, the host's angiogenic response is also genetically regulated. Consequently, applying the principle of antiangiogenesis to the treatment of malignant tumors serves as a foundational pillar of therapy.

Microvessel density (MVD) is the number of blood vessels per unit area and it is the parameter most frequently used to quantify intratumoral angiogenesis. Microvessel density is an indicator of the intensity of angiogenesis (4).

Different types of tumors exhibit different levels of angiogenesis (5). The kidneys are highly vascularized organs; according to several studies, renal cell carcinoma displays a significantly higher microvessel density than lung, breast, colon, or ovarian carcinomas (6).

AIM

The aim of the study was to determine the relationship between angiogenesis and various histopathologic features in renal cell carcinoma and also to evaluate the prognostic significance of angiogenesis.

MATERIALS AND METHODS

The study included 120 patients of both sexes with renal cell carcinoma confirmed by histopathological analysis following nephrectomy. All patients underwent surgery at the Urology Clinic of the Clinical Center University of Sarajevo. Participants signed informed consent forms in compliance with the Declaration of Helsinki. The study was approved by the Ethics Committees of the Clinical Center University of Sarajevo and the Faculty of Medicine, University of Sarajevo.

To identify neovascular microvessels, the endothelial marker CD105 (Endoglin) was used for immunohistochemical staining. Microvessel density was determined using an Olympus BX40 microscope equipped with a digital camera (2448x1920 pixels resolution) and microphotography software. Vessel density was expressed as the number of immunohistochemically labeled vascular structures within a scanned area of 1.11 mm^2. This study followed the recommendations provided by Weidner regarding microscopic field size and vascular element counting methods (7). Histological preparations were first examined at low magnification (x10) to identify 'hot spots' (areas with the highest concentration of small blood vessels). Individual vessels were then counted at higher magnification (x200), and images were captured via microphotography. The final result for each subject was calculated as the mean value from three visual fields (each 1.11 mm^2); this absolute number was used for further data processing.

RESULTS

Microvessel density was analyzed in relation to histological subtype, pT stage, TNM stage and tumor size.

Table I **The microvessel density in relation to histopathohistological features of the tumor (histological subtype, pT stage, TNM stage and tumor size).**

Tumor characteristic	n	%	MVD-CD105	p	Post hoc test
Histological subtype				[a]<0,001	
Clear cell cRCC	95	79	269		[b]ccRCC i chRCC, p=0.021; [b]ccRCC i pRCC, p=0.008
Papillary pRCC	12	10	123		
Chromophobe chRCC	7	5.8	126		
Collecting duct cdRCC	1	0.8	-		
Unclassified ucRCC	5	4.2	153		
pT stage				[a]0,097	-
pT1a	44	36.7	166		
pT1b	19	15.8	255		
pT2a	3	2.5	157		
pT2b	3	2.5	-		
pT3a pT3b	45 0	37.5 0	278		
pT3c	1	0.8	-		
pT4	5	4.2	166		
TNM stage				[c]0,010	
I	60	50.8	224.85		I i III, p=0.012 II i III, p=0.020 III i IV, p=0.022
II	5	4.2	136.4		
III	43	36.7	297.41		
IV	12	8.3	180.30		
Fuhrman gr. (n=112)				[c]0,688	
1	4	3.6	181.75		-
2	41	36.6	260,61		
3	48	42.9	261.27		
4	19	17.0	232.84		
Tumor size (cm)				[c]0.342	
<4	48	40.0	224.23		
4-6,9	38	31.7	265.05		
7-10	23	19.2	273.71		
>10	11	9.2	208.0		

- value excluded from analysis, collecting duct carcinoma – one case (MVD-CD105 value); aKruskal-Wallis test; b Multiple Pairwise comparison – Dunn's Post-Hoc test; cOne-Way ANOVA; **significance level for two-sided testing p<0.001, * significance level for two-sided testing p<0.00

There was a statistically significant difference in the distribution of the microvessel density values across histological subtypes of kidney cancer. The median MVD value in clear cell carcinoma (269) was higher than those in papillary carcinoma (123) and chromophobe carcinoma (126). A non-parametric Kruskal-Wallis test provided strong evidence of this ($p=0.000475$, $p<0.001$).

Regarding tumor progression, TNM stage II exhibited the lowest median (127), while TNM stage III showed the highest (288). The average MVD-CD105 value in stage III was 297.41, exceeding the averages found in stages I, II, and IV. A parametric one-way ANOVA confirmed a significant difference between the mean MVD-CD105 values across TNM stages ($F(3.116)=3.938$, $p=0.010$) (Table 1).

In correlation with other pathohistological characteristics of the tumors examined in this study, no statistically significant difference was observed in the distribution of MVD values in relation to pT stage, Fuhrman grade, or tumor size.

Table 2 **Average survival in relation to the value of the density of blood vessels (low and moderate value in comparison to high), n=120.**

	Overall survival						
MVD-CD105	Average survival (months)	SEM	95% confidence interval		[1] Log Rank Mantel-Cox		
			Lower value	Upper value	X^2	df	p
Low and moderate (<306)	47.588	2.239	43.199	51.976	4.292	1	0.038
High (≥306)	54.750	2.268	50.305	59.195			
Total	49.975	1.682	46.677	53.273			

When analyzing the five-year average survival of subjects, a statistically significant difference in survival distribution was observed between those with high angiogenesis and those with low or moderate angiogenesis (Log-rank Mantel-Cox, $x2(1,N=120) =4.292$, $p=0.038$). At the end of the five-year follow-up, the average survival for subjects with high endothelial expression of CD105 was 54.75 months (95% CI [50.56–58.94]), which was significantly higher than the survival for subjects with low or moderate expression (47.59 months, 95% CI [43.20-51.98]) (Table 2).

DISCUSSION

The research in this paper is based on the long-standing hypothesis that solid neoplasms require a vascular network for their growth, and that rapidly growing tumors require increased vascularity to sustain that growth. Measuring microvessel density (MVD) is a common method for evaluating angiogenesis. However, assessing angiogenesis is complicated by its dynamic nature; consequently, most studies focus on MVD as a product of angiogenesis captured at a single point in time (8).

In renal cell carcinoma, MVD is highest in the clear cell subtype. Cioca A, et al. and Kinouchi T, et al. reported similar findings in their respective works (9,10).

The results of this study demonstrate that a higher MVD-CD105 is associated with a more advanced TNM stage (with the exception of stage IV, for which the patient sample was small). Since an advanced TNM stage indicates a poorer prognosis, it follows that a higher density of microvascular elements is associated with disease progression and worse clinical outcomes.

Regarding other histopathological characteristics examined in this study, no statistically significant differences were observed in the distribution of MVD values relative to pT stage, Fuhrman grade, or tumor size. These findings contrast with other literature: Kavantzas N, et al. reported that higher MVD is associated with a higher nuclear grade (11), whereas Nativ O, et al. found that MVD is lower in renal cell carcinomas with higher nuclear grades (12). Furthermore, MacLennan et al. observed no statistically significant correlation between MVD elements and pT tumor stage (13).

Based on numerous studies, measuring MVD as a reflection of tumor angiogenesis is considered a potential prognostic factor in renal cell carcinoma. Although it is generally believed that tumors with higher vessel density follow a more aggressive clinical course, some studies have not confirmed that increased vascularity results in poor survival. For instance, Imao T, et al. (14) and Yildiz T, et al. (15) demonstrated that higher MVD in kidney cancer actually correlates with longer survival.

CONCLUSION

The kidney is a highly vascularized organ, and tumor angiogenesis in renal carcinoma is notably high. The highest density of microvascular elements was observed in clear-cell renal carcinoma. Regarding other pathohistological features, a positive correlation with angiogenesis was found only with the TNM stage. Additionally, microvessel density (MVD-CD105) correlates positively with longer overall survival. In conclusion, the results of this study suggest that greater tumor angiogenesis is associated with improved patient survival.

REFERENCES

1. Folkman J. Angiogenesis. Annu Rev Med. 2006;57:1-18. doi:org/10.1146/annurev.med.57.121304.131306
2. Lešin J, Zlopaša G.Plavac A, Stanojević A,Vujić G.Angiogeneza u malignih tumora. Medicus 2008;17(1):143-8. doi:hrcak.srce.hr /38047
3. Auguste P, Lemiere S, Larrieu-Lahargue F, Bikfalvi A. Molecular mechanisms of tumor vascularization. Crit Rev Oncol Hematol. 2005;54(1):53-61. doi:org/10.1016/j.critrevonc.2004.11.006
4. Mattern J,Volm M. Microvessel density and vascular endothelial growth factor expression in human tumors of different localization. Oncol Rep 1996;3(3):465-8. doi: 10.3892/or.3.3.465.
5. Torres Filho IP, Leunig M, Yuan F, Intaglietta M, Jain RK. Noninvasive measurement of microvascular and interstitial oxygen profiles in a human tumor in SCID mice. Proc Natl Acad Sci U SA. 1994;91(6):2081-5. doi:org/10.1073/pnas.91.6.2081.
6. Bauman TM, Huang W, Lee MH, Abel EJ. Neovascularity as a prognostic marker in renal cell carcinoma. Hum Pathol. 2016;57:98-105. doi: 10.1016/j.humpath.2016.07.005.
7. Weidner N. Current pathologic methods for measuring intratumoralmicrovessel density within breast carcinoma and other solid tumors.Breast Cancer Res Treat. 1995;36(2):169-80.99. doi.org/10.1007/bf00666038
8. Jilaveanu LB, Puligandla M,Weiss SA,Wang XW, Zito C, Flaherty KT, et al. Tumor Microvessel Density as a Prognostic Marker in High-Risk Renal Cell Carcinoma Patients Treated on ECOG-ACRIN E2805. Clin Cancer Res. 2017;24(1);217-23. doi: 10.1158/1078-0432.CCR-17-1555.
9. Cioca A, Muntean DL. Bungardean C. CD105 as a tool for assessing microvessel density in renal cell carcinoma. Indian Journal of Pathology and Microbiology. 2019;62(2):239-43.doi: org/10.4103/ijpm.ijpm_773_17
10. Kinouchi T, Mano M, Matsuoka I, Kodama S, Aoki T, Okamoto M, et al. Immature tumor angiogenesis in high-grade and high-stage renal cell carcinoma. Urology. 2003;62(4):765-70. doi: 10.1016/s0090-4295(03)00512-0.
11. Kavantzas N, Paraskevakou H, Tseleni-Balafouta S, Aroni K, Athanassiades P, Agrogiannis G, et al. Association between microvessel density and histologic grade in renal cell carcinomas. Pathol Oncol Res. 2007;13(2):145-8. doi: 10.1007/BF02893490.
12. Nativ O, Sabo E, Reiss A, Wald M, Madjar S, Moskovitz B. Clinical significance of tumor angiogenesis in patients with localized renal cell carcinoma. Urology. 1998;51(5):693-6. doi:10.1016/s0090-4295(98)00019-3.
13. MacLennan GT, Bostwick DG. Microvessel density in renal cell carcinoma: lack of prognostic significance. Urology. 1995;46(1):27-30. doi: 10.1016/S0090-4295(99)80153-8.
14. Imao T, Egawa M,Takashima H, Koshida K, Namiki M. Inverse correlation of microvessel density with metastasis and prognosis in renal cell carcinoma. Int J Urol. 2004;11(11):948-53. doi: 10.1111/j.1442-2042.2004.00931.x.
15. Yildiz E, Ayan S, Goze F, Gokce G, Gultekin EY. Relation of microvessel density with microvascular invasion, metastasis and prognosis in renal cell carcinoma. BJU Int. 2008;101(6):758-64.doi: 10.1111/j.1464-410X.2007.07318.x.

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Clinical Justification and Impact of Artificial Intelligence in Dermatology Practice: Evidence, Benefits, and Limitations

Opravdanost i učinak umjetne inteligencije u kliničkoj dermatologiji: dokazi, koristi i ograničenja

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ABSTRACT

The application of modern technology, particularly artificial intelligence (AI), represents a major advancement in contemporary clinical dermatology. The development of machine learning and deep learning algorithms has enabled high-accuracy analysis of dermatological images, especially in dermoscopy and early detection of malignant skin lesions. The aim of this paper is to assess the justification and clinical impact of artificial intelligence in dermatology, with an emphasis on diagnostic reliability and clinical applicability. This paper is designed as a review of relevant scientific literature published between 2018 and 2025, based on searches of the PubMed/MEDLINE and Google Scholar databases. The analyzed studies demonstrate that AI-based systems can achieve diagnostic accuracy comparable to that of experienced dermatologists in selected clinical scenarios, particularly in distinguishing benign from malignant lesions. Despite these promising findings, several limitations remain, including data bias and the need for further clinical validation in real-world settings.

Keywords: artificial intelligence; dermatology; dermoscopy; teledermatology; diagnostic accuracy

SAŽETAK

Primjena moderne tehnologije, posebno umjetne inteligencije (UI), predstavlja značajan iskorak u savremenoj kliničkoj dermatologiji. Razvoj algoritama mašinskog i dubokog učenja omogućio je analizu dermatoloških slika s visokim stepenom tačnosti, naročito u oblasti dermoskopije i ranog otkrivanja malignih kožnih lezija. Cilj ovog rada je procijeniti opravdanost i učinak primjene umjetne inteligencije u kliničkoj dermatologiji, s fokusom na dijagnostičku pouzdanost i kliničku primjenjivost. Rad je koncipiran kao pregled relevantne naučne literature objavljene u periodu od 2018. do 2025. godine, pretraživanjem baza PubMed/MEDLINE i Google Scholar. Analizirane studije ukazuju da sistemi zasnovani na umjetnoj inteligenciji u određenim kliničkim situacijama postižu dijagnostičku tačnost uporedivu s iskusnim dermatolozima, posebno u razlikovanju benignih i malignih lezija. Uprkos obećavajućim rezultatima, primjena umjetne inteligencije suočava se s ograničenjima kao što su pristrasnost podataka i potreba za dodatnom kliničkom validacijom.

Ključne riječi: umjetna inteligencija; dermatologija; dermoskopija; teledermatologija; dijagnostička tačnost

INTRODUCTION

Dermatology is a visually driven medical specialty in which clinical decision-making largely depends on the interpretation of morphological patterns of skin lesions. The increasing incidence of skin cancer worldwide, particularly melanoma and non-melanoma skin cancers, has placed additional demands on dermatological services and highlighted the need for efficient and accurate diagnostic support tools (1). In this context, modern technology and artificial intelligence (AI) have emerged as promising solutions to improve diagnostic accuracy and clinical workflow in dermatology (2).

Artificial intelligence, particularly machine learning and deep learning techniques based on convolutional neural networks, has demonstrated remarkable performance in image recognition tasks. These technologies have been increasingly applied to dermatological imaging, including clinical photographs and dermoscopic images, enabling automated classification of skin lesions (3). Several studies have shown that AI-based systems can achieve diagnostic accuracy comparable to that of experienced dermatologists in differentiating benign from malignant skin lesions (4).

The application of artificial intelligence in dermatology extends beyond skin cancer detection. AI systems are increasingly used in teledermatology, inflammatory skin disease assessment, treatment monitoring, and clinical decision support, contributing to improved accessibility and efficiency of dermatological care (5). Particularly in regions with limited access to specialist dermatologists, AI-supported teledermatology may reduce diagnostic delays and improve patient outcomes (6).

Despite these advances, the integration of artificial intelligence into routine clinical practice remains challenging. Concerns have been raised regarding data bias, lack of transparency of algorithmic decision-making, variability in image acquisition, and limited generalizability across different populations and clinical settings (7). Furthermore, ethical, legal, and regulatory issues continue to shape the responsible implementation of AI technologies in healthcare (8). Therefore, the aim of this paper is to analyze the justification and clinical impact of artificial intelligence in modern dermatology, focusing on its diagnostic performance, clinical applicability, and existing limitations, based on current scientific evidence.

MATERIALS AND METHODS

This paper was designed as a structured narrative review of the scientific literature focusing on the application of artificial intelligence in clinical dermatology. The review methodology was selected in order to systematically summarize current evidence regarding diagnostic performance, clinical applicability, and limitations of AI-based systems in dermatological practice (9).

A comprehensive literature search was conducted using the PubMed/MEDLINE and Google Scholar databases. The search strategy included combinations of the following keywords: artificial intelligence, machine learning, deep learning, dermatology, skin cancer, dermoscopy, and teledermatology. The search was limited to articles published between 2018 and 2025 in the English language, ensuring relevance to contemporary clinical practice (10).

Studies were included if they investigated the use of artificial intelligence for the diagnosis, classification, or clinical management of dermatological conditions. Both clinical and dermoscopic image-based studies, as well as review articles addressing AI implementation in dermatology, were considered eligible. Exclusion criteria comprised case reports, editorials, conference abstracts without full-text availability, and studies lacking clear methodological descriptions or outcome measures (11).

The selected publications were screened based on titles and abstracts, followed by full-text assessment. Data extraction focused on study design, type of artificial intelligence model, dermatological application, reported diagnostic performance metrics, and identified clinical limitations. Given the review-based nature of this study, no direct involvement of human participants or experimental procedures was undertaken; therefore, ethical approval was not required (12).

The body of literature included in this review consisted of peer-reviewed original research articles and high-quality review papers addressing the application of artificial intelligence in clinical dermatology. The included studies encompassed randomized controlled trials, prospective and retrospective observational studies, diagnostic accuracy studies, validation studies of artificial intelligence–based systems, as well as systematic and narrative reviews relevant to dermatological imaging, dermoscopy, teledermatology, and inflammatory skin diseases. As this work was designed as a structured narrative review rather than a systematic review or meta-analysis, the emphasis was placed on qualitative synthesis of evidence, methodological characteristics, and reported clinical outcomes rather than quantitative pooling of study results.
In total, 26 peer-reviewed publications were reviewed and synthesized in this structured narrative review, comprising original research articles and review papers addressing the clinical application, performance, and limitations of artificial intelligence in dermatology.

RESULTS

The reviewed literature demonstrates a rapid expansion of artificial intelligence applications in clinical dermatology, with the strongest evidence reported in the field of skin cancer detection. Most analyzed studies focused on convolutional neural network-based models trained on clinical and dermoscopic images for lesion classification (13). Across multiple datasets, AI-based systems achieved high diagnostic performance, with reported area under the curve (AUC) values frequently exceeding 0.85, particularly for melanoma detection (14).

Comparative studies consistently showed that artificial intel ligence systems can perform at a level comparable to experienced dermatologists in distinguishing malignant from benign skin lesions under controlled conditions (15). In some experimental settings, AI-assisted decision-making improved overall diagnostic accuracy when used as a support tool rather than a standalone system (16).

Beyond oncological applications, artificial intelligence demonstrated promising results in teledermatology. AI-supported image triage systems enabled prioritization of high-risk lesions and reduced waiting times for specialist consultation, particularly in resource-limited settings (17). Studies evaluating inflammatory and chronic skin diseases, such as psoriasis and acne, reported improved disease severity assessment and treatment monitoring using AI-based image analysis tools (18).

However, variability in reported outcomes was observed across studies. Diagnostic performance was influenced by image quality, dataset diversity, and patient skin phototype distribution (19). Several studies highlighted reduced accuracy when AI models were applied to external datasets not represented during training, indicating limited generalizability (20).

Overall, the results indicate that artificial intelligence has a measurable positive impact on diagnostic efficiency and clinical workflow in dermatology, particularly when integrated as a decision-support tool. Nevertheless, the effectiveness of AI systems remains highly dependent on data quality, validation methodology, and clinical context. The included literature predominantly comprised diagnostic accuracy and validation studies evaluating artificial intelligence–based systems in dermatology, with a particular focus on image-based lesion classification and clinical decision support.

DISCUSSION

The findings summarized in this review confirm that artificial intelligence is becoming an increasingly relevant component of modern dermatological practice, particularly in image-based diagnostics. Recent studies have consistently demonstrated that deep learning models trained on large-scale dermatological image datasets are capable of recognizing complex visual patterns that may be subtle or difficult to detect in routine clinical examinations. These capabilities position artificial intelligence as a valuable adjunct to dermatologists, especially in settings characterized by high patient volumes and limited specialist availability (21).

One of the most important aspects highlighted in contemporary research is the distinction between experimental performance and real-world clinical utility. While many artificial intelligence systems report high diagnostic accuracy under controlled conditions, their performance may decline when exposed to heterogeneous clinical environments, variable image quality, and diverse patient populations. Several authors emphasize that prospective validation and testing across multiple clinical settings are essential before widespread clinical adoption can be justified (22).

Another critical issue discussed in recent literature concerns the interpretability and transparency of artificial intelligence systems. Black-box decision-making remains a significant barrier to clinician trust and acceptance. Studies focusing on explainable artificial intelligence argue that dermatologists are more likely to adopt AI tools when algorithmic outputs are accompanied by visual explanations or confidence estimates that can be integrated into clinical reasoning (23). Without such interpretability, AI systems risk being perceived as opaque tools that undermine rather than support clinical judgment. The role of artificial intelligence in dermatology also raises important questions related to bias and health equity. Emerging evidence suggests that algorithms trained predominantly on images from lighter skin phototypes may demonstrate reduced accuracy in patients with darker skin, potentially exacerbating existing disparities in dermatological care. Addressing these limitations requires deliberate efforts to diversify training datasets and to evaluate algorithmic performance across different demographic groups (24).

From a clinical workflow perspective, artificial intelligence shows particular promise in triage and prioritization of dermatological cases. Recent evaluations of AI-assisted referral systems indicate that automated risk stratification can improve efficiency by identifying high-risk lesions earlier, thereby optimizing specialist workload and reducing diagnostic delays. However, these systems must be carefully integrated into existing healthcare structures to avoid overreliance on automated outputs (25).

Current consensus-oriented publications underline that artificial intelligence should be regarded as a supportive technology rather than a replacement for dermatologists. The successful implementation of AI in dermatology depends on interdisciplinary collaboration between clinicians, data scientists, and regulatory authorities, as well as ongoing monitoring of clinical performance after deployment. Ethical oversight, regulatory approval, and continuous education of healthcare professionals are essential to ensure that artificial intelligence contributes positively to patient outcomes and maintains trust in dermatological care (26).

CONCLUSION

Artificial intelligence has strong potential to support clinical dermatology, especially in image-based assessment of skin lesions, triage in teledermatology, and decision support. Although high diagnostic performance is frequently reported, real-world effectiveness depends on robust external validation, transparent reporting, and continuous monitoring after implementation. AI tools should be integrated as an adjunct to clinical reasoning, with dermatologist oversight retained in diagnostic and treatment decisions. Future efforts should prioritize representative datasets, prospective clinical studies, and practical evaluation of safety, workflow impact, and equity. With appropriate governance and clinical integration, AI may improve efficiency and access to dermatological care.

REFERENCES

1. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, Hay RJ, Langan SM, et al. Global skin disease morbidity and mortality: an update from the Global Burden of Disease Study 2013. JAMA Dermatol. 2017;153(5):406-12. doi:10.1001/jamadermatol.2016.5538
2. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44-56. doi:10.1038/s41591-018-0300-7
3. Litjens G, Kooi T, Bejnordi BE, Setio AAA, Ciompi F, Ghafoorian M, et al. A survey on deep learning in medical image analysis. Med Image Anal. 2017;42:60-88. doi:10.1016/j.media.2017.07.005
4. Haenssle HA, Fink C, Schneiderbauer R, Toberer F, Buhl T, Blum A, et al. Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists. Ann Oncol. 2018;29(8):1836-42. doi:10.1093/annonc/mdy166
5. Tschandl P, Rinner C, Apalla Z, Argenziano G, Codella N, Halpern A, et al. Human-computer collaboration for skin cancer recognition. Nat Med. 2020;26(8):1229-34. doi:10.1038/s41591-020-0942-0
6. Ebner C, Wurm EM, Binder B, Kittler H, Lozzi GP, Massone C, et al. Mobile teledermatology: a feasibility study of 58 subjects using mobile phones. J Telemed Telecare. 2008;14(1):2-7. doi:10.1258/jtt.2007.070302
7. Melarkode N, Srinivasan K, Qaisar SM, Plawiak P. AI-powered diagnosis of skin cancer: a contemporary review, open challenges and future research directions. Cancers (Basel). 2023;15(4):1183. doi:10.3390/cancers15041183
8. Price WN 2nd, Cohen IG. Privacy in the age of medical big data. Nat Med. 2019;25(1):37-43. doi:10.1038/s41591-018-0272-7
9. Greenhalgh T, Thorne S, Malterud K. Time to challenge the spurious hierarchy of systematic over narrative reviews? Eur J Clin Invest. 2018;48(6):e12931. doi:10.1111/eci.12931
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-34. doi:10.1016/j.jclinepi.2009.06.006
11. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8(1):19-32. doi:10.1080/1364557032000119616
12. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4. doi:10.1001/jama.2013.281053
13. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017;542(7639):115-8. doi:10.1038/nature21056
14. Fink C, Blum A, Buhl T, Mitteldorf C, Hofmann-Wellenhof R, Deinlein T, et al. Diagnostic performance of a deep learning convolutional neural network in the differentiation of combined naevi and melanomas. J Eur Acad Dermatol Venereol. 2020;34(6):1355-61. doi:10.1111/jdv.16165

15. Tschandl P, Codella N, Akay BN, Argenziano G, Braun RP, Cabo H, et al. Comparison of the accuracy of human readers versus machine-learning algorithms for pigmented skin lesion classification: an open, web-based, international, diagnostic study. Lancet Oncol. 2019;20(7):938-47. doi:10.1016/S1470-2045(19)30333-X
16. Magrabi F, Ammenwerth E, Brender McNair J, De Keizer NF, Hyppönen H, Nykänen P, et al. Artificial intelligence in clinical decision support: challenges for evaluating AI and practical implications. Yearb Med Inform. 2019;28(1):128-34. doi:10.1055/s-0039-1677903
17. Finnane A, Dallest K, Janda M, Soyer HP. Teledermatology for the diagnosis and management of skin cancer: a systematic review. JAMA Dermatol. 2017;153(3):319-27. doi:10.1001/jamadermatol.2016.4361
18. Shrivastava VK, Londhe ND, Sonawane RS, Suri JS. Computer-aided diagnosis of psoriasis skin images with HOS, texture and color features: a first comparative study of its kind. Comput Methods Programs Biomed. 2016;126:98-109. doi:10.1016/j.cmpb.2015.11.013
19. Adamson AS, Smith A. Machine learning and health care disparities in dermatology. JAMA Dermatol. 2018;154(11):1247-8. doi:10.1001/jamadermatol.2018.2348
20. Daneshjou R, Smith MP, Sun MD, Rotemberg V, Zou J. Lack of transparency and potential bias in artificial intelligence data sets and algorithms: a scoping review. JAMA Dermatol. 2021;157(11):1362-9. doi:10.1001/jamadermatol.2021.3129
21. Brinker TJ, Hekler A, Enk AH, Klode J, Hauschild A, Berking C, et al. Deep learning outperformed 136 of 157 dermatologists in a head-to-head dermoscopic melanoma image classification task. Eur J Cancer. 2019;113:47-54. doi:10.1016/j.ejca.2019.04.001
22. Brancaccio G, Balato A, Malvehy J, Puig S, Argenziano G, Kittler H. Artificial intelligence in skin cancer diagnosis: a reality check. J Invest Dermatol. 2024;144(3):492-99. doi:10.1016/j.jid.2023.10.004
23. Tjoa E, Guan C. A survey on explainable artificial intelligence (XAI): toward medical XAI. IEEE Trans Neural Netw Learn Syst. 2021;32(11):4793-813. doi:10.1109/TNNLS.2020.3027314
24. Daneshjou R, Vodrahalli K, Novoa RA, Jenkins M, Liang W, Rotemberg V, et al. Disparities in dermatology AI performance on a diverse, curated clinical image set. Sci Adv. 2022;8(32):eabq6147. doi:10.1126/sciadv.abq6147
25. Dildar M, Akram S, Irfan M, Khan HU, Ramzan M, Mahmood AR, et al. Skin cancer detection: a review using deep learning techniques. Int J Environ Res Public Health. 2021;18(10):5479. doi:10.3390/ijerph18105479
26. Kelly CJ, Karthikesalingam A, Suleyman M, Corrado G, King D. Key challenges for delivering clinical impact with artificial intelligence. BMC Med. 2019;17(1):195. doi:10.1186/s12916-019-1426-2

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A Successful Pregnancy after Surgical Treatment Adenocarcinoma Endometrioid G2 (pT1a) of the Ovary

Uspješna trudnoća nakon hirurškog liječenja endometrioidnog adenokarcinoma jajnika G2 (pT1a)

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ABSTRACT

Introduction: primary treatment includes comprehensive cytoreductive surgery with complete staging followed by adjuvant treatment or observation. Fertility-sparing surgery is a selection for stage IA-IC1 tumors, with half of recurrences in these cases appearing in the contralateral ovary and therefore amenable to rescue by subsequent surgery. Case report: the patient was 45 years old and with her 4th pregnancy. She had 3 spontaneous abortions. She arrived to the Clinic for an elective caesarean section at 38 + 0. She got pregnant naturally and had regular gynecological check-ups. Ultrasound examination: BPD 99, FL 78, AFI 24/4, FHR positive +, RI au 0.54, anterior placenta position. In 2022 she had left adnexectomy (PHD: Adenocarcinoma endometrioses G2 ovarii lateris sinistri pT1a Figo stage Ia). The patient refused chemotherapy. Conclusion: the patient became pregnant naturally after two years of surgical treatment (left adnexectomy). She gave birth to a male child by cesarean section. Both patient and her baby were feeling well. PHD analysis (biopsy of the right ovary and a partial omentectomy) showed there were no signs of disease recurrence, although she refused chemotherapy. Currently, her gynecological status is normal without any abnormalities. The patient was satisfied with the successful delivery after three spontaneous abortions without reducing the success of cancer treatment.

Keywords: ovarian cancer, endometrioid adenocarcinoma, fertility-sparing surgery, pregnancy

SAŽETAK

Uvod: primarni tretman uključuje sveobuhvatnu citoreduktivnu operaciju uz potpuno određivanje stadija, nakon čega slijedi adjuvantni tretman ili opservacija. Operacija očuvanja plodnosti je za tumore stadija IA-IC1, pri čemu se polovina recidiva u ovim slučajevima javlja u kontralateralnom jajniku i stoga ih je moguće spasiti naknadnom operacijom. Prikaz slučaja: pacijentica 45 godina, četvrta trudnoća. Ranije je imala 3 spontana pobačaja. Došla je u kliniku na elektivni carski rez u 38. sedmici trudnoće. Zatrudnila je prirodnim putem i trudnoća redovno kontrolisana. Ultrazvučni pregled: BPD 99, FL 78, AFI 24/4, FHR pozitivan +, RI au 0.54, posteljica prednji zid. Imala je operativni zahvat 2022. godine, učinjena lijeva adneksektomija (PHD: Adenocarcinoma endometrioses G2 ovarii lateris sinistri pT1a Figo stadij Ia). Pacijentica je odbila kemoterapiju. Zaključak: pacijentica je zatrudnila prirodnim putem nakon dvije godine od hirurškog tretmana (lijeva adneksektomija). Rodila je muško dijete carskim rezom. Pacijentica i beba su bili dobro. PHD analiza (biopsija desnog jajnika i parcijalna omentektomija) nije pokazala znakove recidiva bolesti, iako je odbila kemoterapiju. Trenutno je njen ginekološki status uredan, bez ikakve prisutne patologije. Pacijentica je zadovoljna uspješnim porođajem nakon tri spontana pobačaja bez smanjenja uspjeha liječenja karcinoma.

Ključne riječi: karcinom jajnika, endometrioidni adenokarcinom, hirurgija očuvanja plodnosti, trudnoća

INTRODUCTION

Ovarian cancer is the 8th most common cancer in women around the world (1), a heterogeneous disease which can be classified in epithelial and non-epithelial origin. Among epithelial ovarian cancer (EOC), high-grade serous carcinoma is the most common, comprising around 70% of all cases. On the other side, rare epithelial tumors include endometroid, mucinous, clear cell carcinomas (CCC), and carcinosarcomas. Among those with non-epithelial origin, germ cell tumors and sex cord-stromal tumors are most frequent ones (1).

Primary treatment includes complete cytoreductive surgery with comprehensive staging followed by adjuvant treatment or observation. Fertility-sparing surgery is an option for stage IA-IC1 tumors, with a half of recurrences in these cases occurring in the contralateral ovary and therefore amenable to rescue by subsequent surgery (1).

Stages IA and IB (T1a or T1b, N0, M0): The treatment after surgery depends on how the cancer cells look in the lab (called the tumor grade) (2).

For grade 1 (also called low grade) tumors, most women do not need any treatment after surgery. Women who want to be able to have children after treatment might be given the option of having an initial surgery that removes only the ovary containing the cancer along with the fallopian tube on the same side (2).

For grade 2 (high grade) tumors, patients are either watched closely after surgery without further treatment, or they are treated with chemotherapy (chemo). The most often used chemo is carboplatin and paclitaxel (Taxol) for 3-6 cycles, but cisplatin can be used instead of carboplatin, and docetaxel (Taxotere) can be used instead of paclitaxel (2).

For grade 3 (high grade) tumors, the treatment usually includes the same chemotherapy that is given for grade 2 Stage IA and IB cancers (2).

CASE REPORT

The case related to a 45-years-old female in her 4th pregnancy. She previously had 3 spontaneous abortions. She arrived to the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo, for an elective caesarean section at 38 + 0. She got pregnant naturally and had regular gynecological check-ups. Ultrasound examination: BPD 99, FL 78, AFI 24/4, FHR positive +, RI au 0.54, anterior placenta position.

Menarche: 14, the last menstrual period date: 23 January 2024, previous obstetric history: 3 spontaneous abortions.
Unknown drug allergies and blood type B -. From earlier period she had mutation MTHFR heterozygous and PAI-1. She took Methyldopa a 250 mg 3x2 tablet daily during the last month of pregnancy. She had negative history on infection diseases, but in 2022 she had left adnexectomy.

History of family diseases: mother of the patient had heart surgery and her father had hypertension.

Table 1 **Medical history prior to 4th pregnancy.**

Feb. 2022	Ultrasound examination: Uterus is in AVF position with measuring 76x60 mm, endometrium is 8 mm hyperechoic. On the right side of the uterus is an anechoic tumor with a diameter of 70x30 mm with intraluminal proliferation of 27 mm. On the other side, left ovary is with neat/orderly structure. There is no free liquid in Cavum Douglasi. After the review, it is referred to the operational committee.
April 2022	She had left adnexectomy and the removed material was sent for PHD analysis.
May 2022	PHD: Adenocarcinoma endometrioses G2 ovarii lateris sinistri pT1a Figo stage Ia CT scan of the abdomen and pelvis: Status post left adnexectomy with no definite signs of recurrence, in the projection of the right adnexitis is a cystic change with a diameter of 15 mm. CA 125 28.1 IU/mL
June 2022	She was examined by an oncologist who suggested adjuvant chemotherapy T/C protocol of 6 cycles, then a reevaluation with an MRI of the abdomen and pelvis and Ca 125. It was planned to prescribe LHRH agonists during chemotherapy. The patient refused therapy.
August 2022	Mammogram shows no sign of abnormalities. Tumor markers: CEA 2.07 ng/mL, CA 15-3 30.6, CA 125 19.5 IU/mL, HE4 31.7 pmol/L, CA 19-9 16.1 IU/mL, AFP 7.72
Sept. 2022	CT of the abdomen and pelvis was performed. Below results were gathered: Right ovary is more voluminous with regression in the size of the previously described cystic change (9 mm). A Pap smear shows no sign of abnormalities.
Oct. 2022	Ultrasound examination: Uterus is in AVF position with normal size and homogeneous myometrium. Endometrium is a tri-laminar. Left ovary is not visible (status after adnexectomy), right ovary is normal size with polycystic appearance. In Cavum Douglasi is minimal amount of free fluid. Regular oncological check-ups.
Feb. 2023	MRI of abdomen and pelvis was performed. No sure signs of recurrence of the underlying process are seen.
August 2023	MRI of abdomen and pelvis was performed. Status post left adnexectomy, without sure signs of local recurrence of the underlying disease. In right ovary is cyst up to 3 cm in diameter which most likely corresponds to a dominant follicle.

An elective caesarean section was accomplished on October 2024. The patient gave birth to a male newborn. The birth weight was 3900g and birth length was 53 cm with APGAR score 10/10. Both patient and her baby were well and they were discharged three days after the surgery.

Biopsy of the right ovary and a partial omentectomy were performed during the operation. The PHD results of the discarded material showed no sign of any abnormalities.

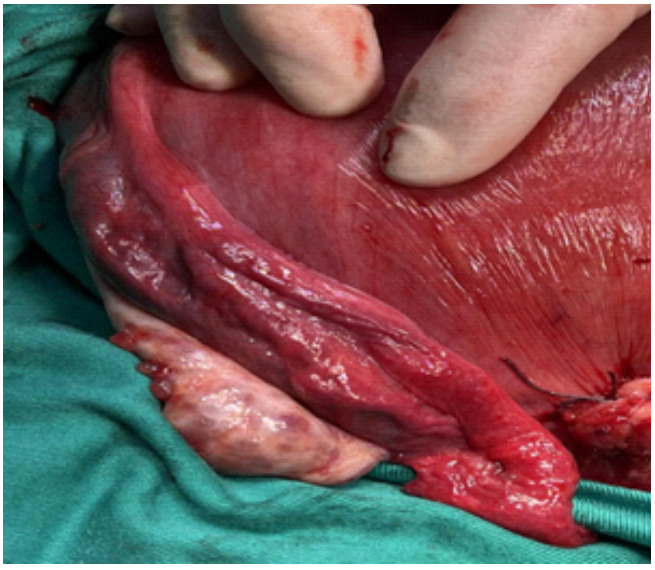

Figure 1 **Anterior side of right ovary.**

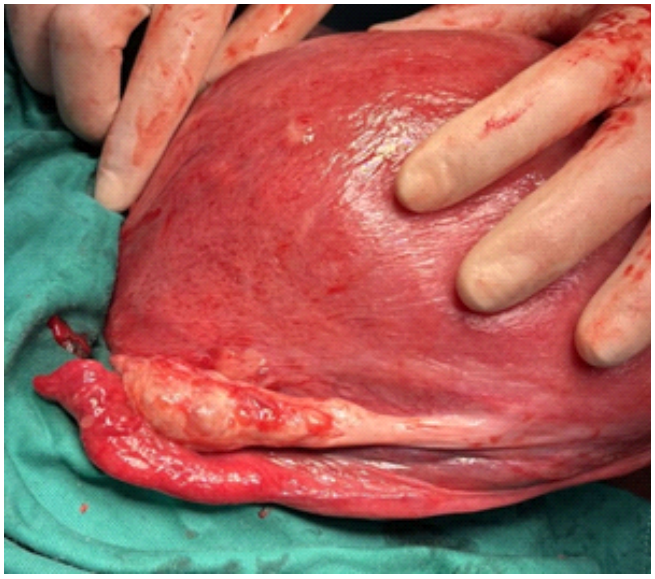

Figure 2 **Posterior side of right ovary.**

DISCUSSION

The most common risk factor for this type of tumor is endometriosis, which increases the risk by about 14 percent (1).
A study by Terada T, et al. (3) showed that atypical endometriosis develops into endometrioid carcinoma after initiation and promotion. The most common malignant tumors arising from ovarian endometriosis are endometrioid adenocarcinoma and clear cell adenocarcinoma.

In a cohort study by Chávarri-GuerraY, et al (1) there were 3552 patients with FIGO stage I endometrioid ovarian carcinoma. The result of the study showed that patients with stage IA/IB, stage 1/2, tumors who had complete surgical staging had a 5-year disease-free survival of over 90% and did not require adjuvant chemotherapy. Patients with stage 3 (any stage) and stage IC-II tumors have a less favorable prognosis, and platinum-based adjuvant chemotherapy should be considered.

In the study by MazinV, et al (4) it was shown that there were no lymph node metastases in patients with primary endometrioid ovarian carcinoma.

Pregnancy and successful delivery were achieved in 4 out of 5 patients who underwent fertility-sparing treatment with synchronous endometrial and ovarian cancers. None of them received chemotherapy (5).

An interesting case report was where the operation (left adnexectomy) was performed at the 18th week of pregnancy. Histopathological analysis showed invasive adenocarcinoma, endometroid well-differentiated type (histological grade I, nuclear grade 2). In the 37th week of gestation, the patient gave birth to a male child by cesarean section. The patient had no subjective complaints for the next 3 years, and laboratory and ultrasound findings were normal (6).

In the study of Nasu K, et al. (7) were included eleven patients younger than 40 years with FIGO stage Ia grade 1 disease, and 2 of these patients were pregnant. Both pregnant women and 5 other patients with stage Ia disease were treated with only unilateral salpingo-oophorectomy. All patients with stage Ia disease had no evidence of recurrence within 5 years.

CONCLUSION

The patient became pregnant naturally after two years of surgical treatment (left adnexectomy). She gave birth to a male child by cesarean section. Both patient and her baby were well. PHD analysis (biopsy of the right ovary and a partial omentectomy) showed there were no signs of disease recurrence, although she refused chemotherapy. Currently, her gynecological status is normal without any abnormalities. The patient was satisfied with the successful delivery after three spontaneous abortions without reducing the success of cancer treatment.

REFERENCES

1. Chávarri-Guerra Y, González-Ochoa E, De-la-Mora-Molina H, Soto-Perez-de-Celis E. Systemic therapy for non-serous ovarian carcinoma. Chin Clin Oncol. 2020;9(4):52. doi: 10.21037/cco-20-36.
2. American Cancer Society: Treatment of Invasive Epithelial Ovarian Cancers, by Stage, 2022. Available on:https://www.cancer.org/cancer/types/ovarian-cancer/treating/by-stage.html
3. Terada T. Endometrioid adenocarcinoma of the ovary arising in atypical endometriosis. Int J Clin Exp Pathol. 2012;5(9):924-7. PMID: 23119109 PMCID: PMC3484489
4. Mazina V, Devins K, Philp L, Bercow AS, James K, Bregar A, et al. Patterns of spread and genetic alterations of primary endometrioid carcinomas of the ovary. Int J Gynecol Cancer. 2023;33(9):1434-9. doi: 10.1136/ijgc-2023-004627.
5. Gama Q, Luo S, Wu P, Wang L, Liu S, Zhang H, et al. The pregnancy and oncology outcome of fertility-sparing management for synchronous primary neoplasm of endometrium and ovary. J Ovarian Res. 2023;16(1):235. doi: 10.1186/s13048-023-01316-w.
6. Zivanović A, Dimitrijević A, Kastratović T, Djurić J, Stanković V, Tanasković I. Ovarian endometroid adenocarcinoma in pregnancy. Vojnosanit Pregl. 2011;68(2):181-4. doi: 10.2298/vsp1102181z
7. Nasu K, Hirota Y, Sugano T, Matsui N, Hayata T, Miyakawa I. Clinical features of epithelial ovarian cancer in young reproductive women. Nihon Sanka Fujinka Gakkai Zasshi. 1995;47(9):911-6. PMID: 7594901

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Rupture of the Vaginal Septum in a Patient with Uterus Didelphys

Ruptura vaginalnog septuma kod pacijentice sa uterus didelphys

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ABSTRACT

Uterus didelphys is a rare congenital Müllerian duct anomaly characterized by duplication of the uterine cavities, cervices, and often the vagina. This report described the case of a 20-year-old woman with profuse vaginal bleeding occurred during sexual intercourse, due to a longitudinal vaginal septum rupture. Surgical intervention successfully achieved hemostasis, and postoperative diagnostic evaluation was recommended. Although fertility is generally preserved in women with uterus didelphys, pregnancies are associated with increased risks of miscarriage, preterm birth, and fetal malpresentation. Management is primarily conservative, with surgical treatment reserved for symptomatic vaginal septa or other associated complications. This case highlights the importance of early recognition, detailed diagnostic assessment, individualized counseling, and careful obstetric surveillance to optimize reproductive outcomes.

Keywords: uterus didelphys, congenital uterine anomaly, longitudinal vaginal septum

SAŽETAK

Uterus didelphys je rijetka kongenitalna anomalija Müllerovog kanala koju karakteriše dupliranje maternicnih šupljina, grlića maternice, a često i vagine. Ovo je prikaz slučaja 20-godišnje žene koja se javila s obilnim vaginalnim krvarenjem koje je nastalo tokom spolnog odnosa. Ruptura longitudinalnog vaginalnog septuma je uzrok krvarenja. Hirurškim zahvatom postignuta je hemostaza, a preporučeno je postoperativna dijagnostika. Iako je plodnost uglavnom očuvana kod žena s uterus didelphys, trudnoće su povezane s povećanim rizikom od pobačaja, prijevremenog porođaja i lošeg položaja djeteta. Liječenje je prvenstveno konzervativno, a hirurška intervencija je potrebna za simptomatske vaginalne septume ili druge komplikacije. Ovaj slučaj naglašava važnost ranog prepoznavanja, detaljne dijagnostike, individualiziranog savjetovanja i pažljivog opstetričkog praćenja kako bi imali što bolje reproduktivne rezultate.

Ključne riječi:uterus didelphys, kongenitalna anomalija maternice, longitudinalni vaginalni septum

CASE REPORT

A 20-year-old woman was brought to the Outpatient Clinic of the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo, by emergency medical services due to profuse vaginal bleeding occurred during sexual intercourse. The bleeding was ongoing for five hours.

On speculum examination, a thick septum-like structure was observed within the vagina, dividing it into two compartments. The cervix could not be visualized. A rupture of the posterior vaginal wall and the vaginal septum was identified, accompanied by active, heavy bleeding. During the examination, the patient collapsed. An intravenous line had already been established, and two infusions were administered. An urgent transfer to the operating room was indicated. Vital signs upon presentation were stable; she was eupneic at rest and afebrile. Her skin and mucous membranes appeared pale. Blood pressure measured 100/60 mmHg.
d.

Menarche occurred at the age of 14. Obstetric history was negative for prior pregnancies or miscarriages. She reported no chronic illnesses, previous surgeries, or known drug allergies. Her blood type was O RhD-negative.

After disinfection of the external genitalia and vagina, the patient was placed under OET anesthesia. Intraoperative speculum examination revealed a longitudinal vaginal septum extending from the vaginal apex to the distal third of the vagina. The right hemivagina was larger and contained an epithelialized cervix; the left hemivagina was smaller, also with an epithelialized cervix. Inspection showed that the lower portion of the septal base, approximately 2 cm in length, had separated from the vaginal wall, and a rupture of the posterior wall of the distal third of the vagina, approximately 3 cm in length, was present, with ongoing active bleeding (Figure 1). Hemostasis was achieved using a continuous suture followed by several interrupted sutures in the standard manner. Hemostasis was complete. Urine in the catheter was clear. The patient awoke in good condition on the operating table, having tolerated the procedure well. A 10 × 10 cm vaginal gauze pack was left in place. Postoperative therapy was initiate

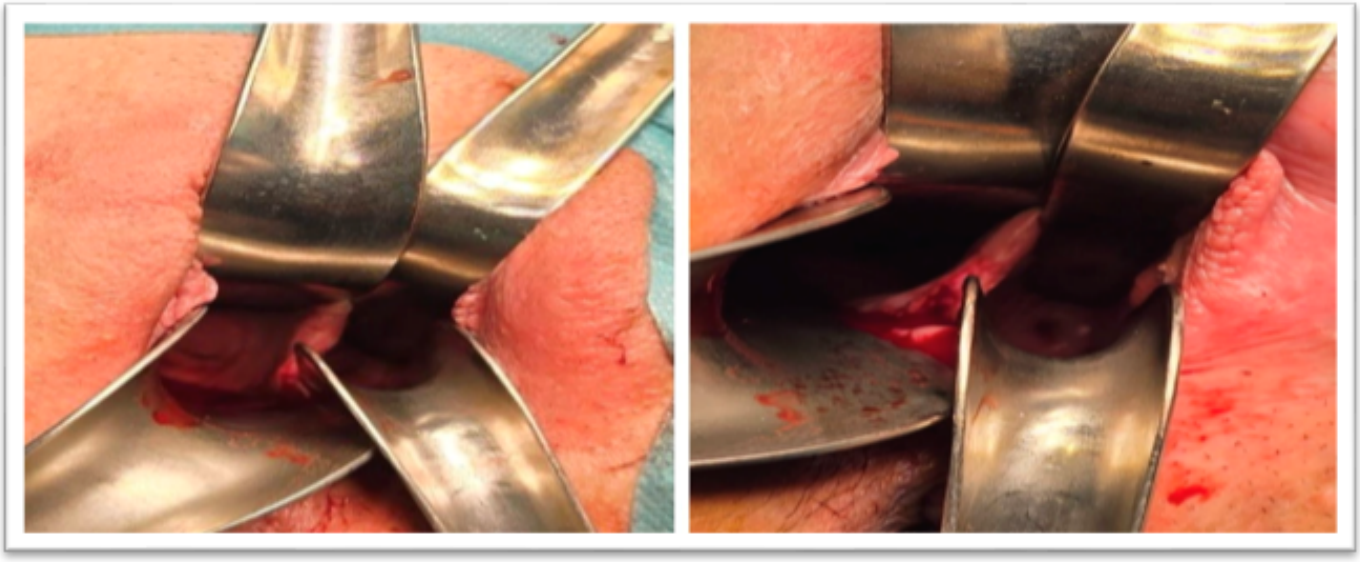

Figure 1 **Two cervixes, longitudinal vaginal septum, two vaginas and rupture of the lower part of the base of the septum.**

During hospitalization, the patient received two units of packed red blood cells of the corresponding blood type and Rh factor.
On the first postoperative day, a pelvic ultrasound examination was performed. The diagnosis and expected course were explained to the patient in detail.

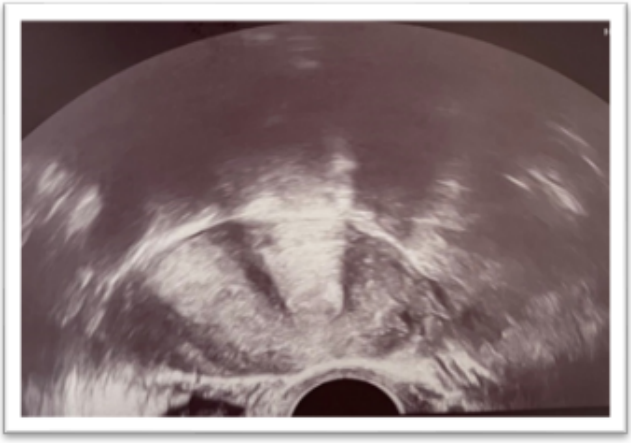

Figure 2

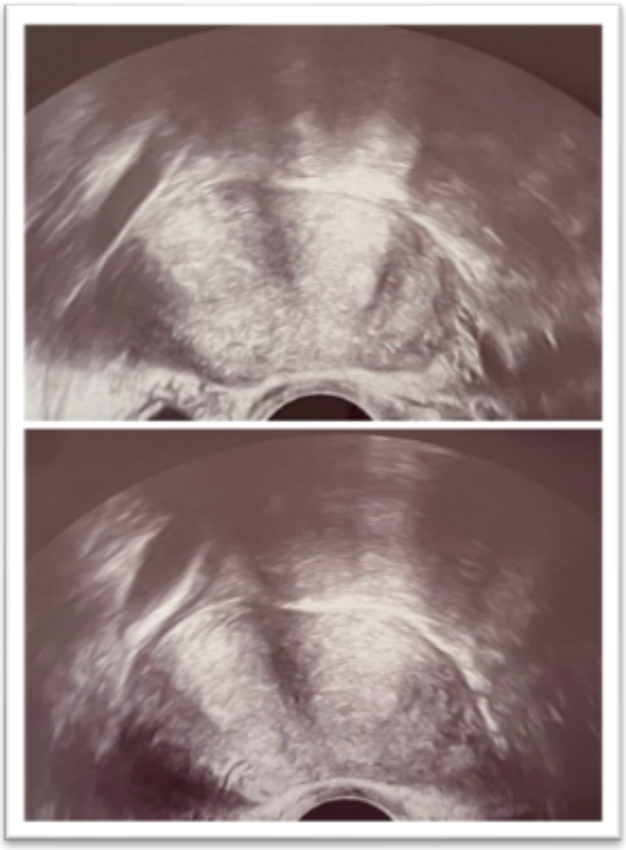

Figure 3

Figure 4

Figure 2,3,4 **Ultrasound of Uterus didelphys**

The patient was discharged from hospital with stable vital signs. She was afebrile, normotensive, eupneic at rest, and without bleeding. The abdomen was soft, and urination and bowel peristalsis were normal.

DISCUSSION

Uterus didelphys is a rare Müllerian duct anomaly resulting from complete failure of fusion of the paramesonephric ducts, leading to duplication of the uterine cavities, cervices, and often the vagina. Accurate diagnosis is essential for appropriate reproductive counseling. Transvaginal two-dimensional ultrasound is typically the initial imaging modality; however, distinguishing among Müllerian anomalies can be challenging. Three-dimensional transvaginal ultrasound has demonstrated superior sensitivity and specificity for characterizing uterine morphology and is increasingly recommended as the first-line diagnostic tool (4).

Despite the anatomical duplication, fertility is generally preserved in women with uterus didelphys, and spontaneous conception is common. Nevertheless, obstetric outcomes are less favorable compared with the general population, with a higher incidence of early pregnancy loss, preterm birth, fetal growth restriction, malpresentation, and cesarean delivery (6). Numerous case reports document successful pregnancies, supporting the possibility of favorable perinatal outcomes with appropriate monitoring. For example, Poudel S, et al., (7) reported a viable preterm delivery at 32 weeks in a primigravida with uterus didelphys, while Imami Y, et al., (8) described an uncomplicated pregnancy culminating in a live birth. Additional reports further confirm successful gestation and delivery across various clinical presentations (9).

Management of uterus didelphys is predominantly conservative, as the anomaly rarely compromises fertility enough to justify reconstructive surgery. Current evidence indicates that surgical intervention offers limited benefit in improving reproductive outcomes and may introduce unnecessary risks, including adhesion formation, uterine rupture, and adverse obstetric sequelae (10). Therefore, management should be individualized, focusing on symptom-directed care rather than routine correction of the uterine morphology.

Surgical treatment is reserved for clearly defined indications. Obstructive anomalies such as a longitudinal vaginal septum causing dyspareunia, recurrent infections, or obstructed menstrual flow represent the most common reasons for intervention, and resection of the vaginal septum is typically curative (11). Conversely, uterine unification procedures such as Strassman metroplasty are rarely indicated in uterus didelphys because the condition involves complete duplication rather than incomplete fusion. The evidence supporting metroplasty is limited to highly selected cases, such as women with recurrent pregnancy loss directly attributable to uterine morphology after exclusion of other etiologies (10).

Importantly, hysteroscopic metroplasty widely used for septate uterus has no therapeutic role in uterus didelphys, as the anomaly consists of two entirely separate uterine cavities without a resectable septum (11). Recognizing this distinction is critical in guiding management decisions.

During pregnancy, care is expectant and centered on obstetric surveillance. Women with uterus didelphys should be managed as high-risk due to increased risks of miscarriage, preterm birth, malpresentation, and the need for cesarean delivery. Recommended monitoring strategies include serial ultrasounds for fetal growth assessment, cervical length surveillance, and early identification of preterm labor (5). Delivery planning should be individualized based on fetal presentation, maternal symptoms, and the anatomical configuration of the cervices and vaginal canal. With appropriate surveillance rather than surgical mod

CONCLUSION

Uterus didelphys may remain undetected until adolescence or early adulthood and may first present with complications such as traumatic rupture of a longitudinal vaginal septum, as demonstrated in this case. Prompt recognition of the underlying Müllerian anomaly and timely surgical repair of the septal rupture enabled effective hemostasis and an uncomplicated postoperative recovery. Although most women with uterus didelphys retain normal fertility, pregnancies carry increased risks of miscarriage, preterm birth, and malpresentation; thus, future pregnancies should be managed as high-risk with appropriate obstetric surveillance. Long-term management is generally conservative, as uterine reconstructive surgery seldom improves reproductive outcomes. However, in patients experiencing persistent dyspareunia, recurrent trauma, or other symptoms related to a longitudinal vaginal septum, elective septal resection may be considered to enhance sexual function and prevent future complications. This case underscores the importance of early diagnosis, detailed imaging, and individualized counseling to optimize reproductive health, sexual well-being, and pregnancy outcomes in women with previously unrecognized congenital uterine anomalies.

REFERENCES

1. Ćwiertnia A, Borzyszkowska D, Golara A, Tuczyńska N, Kozłowski M, Kwiatkowski S, et al. The Impact of Uterus Didelphys on Fertility and Pregnancy. Int J Environ Res Public Health. 2022;19(17):10571. doi:10.3390/ijerph191710571.
2. University of Cape Town, Pathology Learning Centre. Uterus didelphys congenital anomalies. [Internet]. Cape Town: UCT Health; c2020–2025. Available from: https://health.uct.ac.za/pathology-learning-centre/disease-themes-when-things-go-wrong-congenital-anomalies/uterus-didelphys
3. Crowley CM, Botros K, Hegazy IF, O'Donnell E. Uterine didelphys: diagnosis, management and pregnancy outcome. BMJ Case Rep. 2021;14(3):e242233. doi:10.1136/bcr-2021-242233.
4. Ramakrishnan KK, Jerosha S, Subramonian SG, Murugappan M, Natarajan P. Comparing the diagnostic efficacy of 3D ultrasound and MRI in Müllerian anomalies. J Obstet Gynecol India. 2024;74(1):1-7. doi: 10.7759/cureus.70632.
5. Kim MA, Choi JS, Lee JH. Reproductive, obstetric and neonatal outcomes in women with congenital uterine anomalies: A meta-analysis. Clin Exp Obstet Gynecol. 2021;48(1):86-94.
6. Ćwiertnia A. The impact of uterus didelphys on fertility and pregnancy. Pol Ann Med. 2022;29(1):41-5. doi.org/10.3390/jcm10214797.
7. Poudel S, Bhattarai M, Soti H. Successful pregnancy outcome in uterus didelphys: A rare case report. JCMS Nepal. 2023;19(1):174-7. doi: 10.3126/jcmsn.v19i2.55960.
8. Imami Y, Al-Ani M, Al-Samarrai M. Didelphic uterus and pregnancy: A case report and review of the literature. Am J Surg Case Rep. 2024;5(1):22-5. doi. 10.52054/ajscr.v5i7.1713.
9. Dorji N, Wangchuk D, Lepcha S. Uterus didelphys with double vagina diagnosed during pregnancy: Case report. SAGE Open Med Case Rep. 2022;10:2050313X221094253. doi:10.1177/2050313X211072967.
10. Ludwin A, Ludwin I, Kudla M. Reproductive surgery for Müllerian anomalies: A review. Best Pract Res Clin Obstet Gynaecol. 2019;59:106-22. doi:10.1016/j.fertnstert.2019.07.005.
11. Practice Committee of the American Society for Reproductive Medicine. Evidence-based diagnosis and treatment for uterine septum: a guideline. Fertil Steril. 2024;122(2):251-65. doi: 10.1016/j.fertnstert.2024.02.033

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Adaptation and Restoration of Teeth in a Boy with Autism Spectrum Disorder - Diagnostic and Therapeutic Challenges

Adaptacija i sanacija zuba kod dječaka iz autističnog spektra - dijagnostički i terapijski izazovi

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ABSTRACT

This case report describes a ten-year-old boy with autism spectrum disorder (ASD) presenting with pronounced sensory hypersensitivity and limited cooperation in the dental setting. Management involved a structured desensitization protocol, visual supports, behavioural guidance techniques, and gradual adaptation to dental procedures. Diagnostic findings revealed multiple carious lesions, gingivitis, and significant plaque accumulation. The therapeutic approach included caries restoration, polishing, gentle plaque removal, fluoride varnish application, and partial pulpotomy. Follow-up demonstrated a marked improvement in oral hygiene and patient cooperation, achieved without the use of pharmacological sedation. This case highlights the importance of an individualized approach and the effectiveness of non-pharmacological strategies in the dental management of children with ASD.

Keywords:case report, autism, sensory hypersensitivity, dental treatment, behavioral management, caries

SAŽETAK

Prikazani slučaj opisuje desetogodišnjeg dječaka s poremećajem iz autističnog spektra (ASD), izrazite senzorne hipersenzitivnosti i ograničene saradljivosti u stomatološkom okruženju. Prikazan je pristup koji je uključio desenzibilizacijski protokol, vizuelnu podršku, tehnike ponašajnog vođenja, te postupnu adaptaciju na stomatološke procedure. Dijagnostički nalazi uključivali su multiple karijesne lezije, gingivitis i prisutne naslage. Terapijski pristup obuhvatio je sanaciju karijesa, poliranje, čišćenje mekih naslaga, aplikaciju fluoridnog laka i parcijalnu pulpotomiju. Tok praćenja ukazuje na značajno poboljšanje oralne higijene i saradljivosti, bez potrebe za farmakološkom sedacijom. Slučaj naglašava važnost individualiziranog pristupa i nefarmakoloških tehnika u tretmanu djece s ASD-om.

Ključne riječi: prikaz slučaja, autizam, senzorna preosjetljivost, stomatološki tretman, upravljanje ponašanjem, karijes

INTRODUCTION

Children diagnosed with autism spectrum disorder (ASD) represent a particularly specific and challenging group of patients in dental practice. Their characteristic difficulties often include sensory hypersensitivity, increased anxiety, communication barriers, and resistance to unfamiliar routines. Consequently, dental procedures require a multidisciplinary approach involving adapted behavioural management techniques, careful preparation, and frequently modified therapeutic protocols. Numerous studies emphasize the importance of an individualized approach that integrates psychological, educational, and pharmacological strategies to achieve effective oral health care (1,2).

Children with ASD have a documented increased risk of dental caries, gingivitis, parafunctional habits, oral infections, and traumatic lesions (3). Factors contributing to this elevated risk include selective dietary habits, reduced tolerance for oral hygiene procedures, limited motor skills, insufficient parental education, and difficulties in accessing dental care. Therefore, interventions must be structured, consistent, and supported by visual aids.

Objective assessments of oral health improvement are carried out by monitoring the reduction in dental plaque index values and gingival bleeding on probing, as standardized clinical parameters of oral hygiene and health.

CASE REPORT

The patient was a 10-year-old boy diagnosed with autism spectrum disorder, non-verbal and exhibiting pronounced sensory hypersensitivity, particularly to facial touch and the sound of dental instruments. His parents report longstanding difficulties with maintaining oral hygiene, limited cooperation and persistent avoidance of dental visits.

Clinical examination revealed multiple decay lesions on tooth 5, deep caries on tooth 75, early buccal carious lesions on teeth 16 and 26, gingivitis and significant plaque accumulation (Figure 1). The initial appointment was carried out without therapeutic intervention, using a desensitisation protocol involving a visual sequence of steps, modelling procedures on the parent and showing photographs of dental instruments.

At the second appointment, using the "tell–show–do" technique, the patient tolerated polishing, removal of soft plaque and application of fluoride varnish. After four visits, full cooperation was achieved for short intervals of 5-7 minutes, enabling restoration of teeth 55 and 75 under local anaesthesia. A partial pulpotomy with glass-ionomer restoration was performed on tooth 75 due to the depth of the carious lesion (Figure 2).

The parents were trained in using a visual brushing routine and modified sensory-stimulation techniques. After one month, a notable improvement in oral hygiene and a reduction in gingivitis were recorded (Figure 3).

Figure 1 **Initial condition with plaque, gingivitis, and bleeding.**

Figure 2 **Caries treated with a glass ionomer filling.**

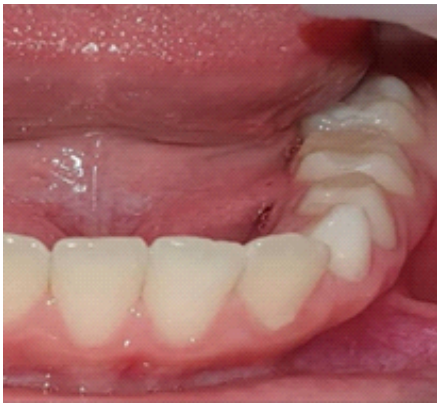

Figure 3 **Patient rehabilitated with no presence of plaque or bleeding.**

DISCUSSION

In line with existing literature, the key factor for successful dental treatment of children with autism spectrum disorder (ASD) lies in personalized treatment planning and the application of psychological strategies. Systematic reviews indicate that visual supports, modelling, and gradual desensitization significantly improve patient cooperation, while visual guidance enhances the ability of children with ASD to perform independent oral hygiene practices (4,5).

In cases of pronounced anxiety, pharmacological sedation may represent a safe and effective option; however, it is recommended only after all non-pharmacological approaches have been exhausted. General anesthesia is reserved for extensive procedures or for children with the most severe forms of autism (6,7).

Recent studies confirm that children with ASD are at increased risk of developing dental caries and periodontal diseases due to dietary habits, oral behaviour patterns, and sensory barriers (8,9). Large meta-analyses further demonstrate that oral health outcomes in children with ASD are poorer compared with those of their neurotypical peers (10).

This case report clearly demonstrates that a structured environment, the use of visual materials, calm communication, and short treatment intervals can gradually increase tolerance and cooperation. These findings are consistent with evidence indicating the long-term benefits of systematic desensitization without the need for pharmacological sedation, representing an optimal outcome for children without severe medical comorbidities (11).

CONCLUSION

Children with autism spectrum disorder have distinct dental care needs and require an individualized, carefully tailored approach. Successful treatment depends on appropriate preparation, flexible therapeutic planning, visual supports, and behavioural techniques that facilitate desensitization and enhance cooperation. This case demonstrates that comprehensive dental treatment and significant improvement in oral health can be achieved using non-pharmacological methods, in full accordance with current scientific evidence.

REFERENCES

1. Al-Beltagi M, Al Zahrani AA, Mani BS, Hantash EM, Saeed NK, Bediwy AS, et al. Challenges and solutions in managing dental problems in children with autism. World J Clin Pediatr. 2025;14(3):106778. doi: 10.5409/wjcp.v14.i3.106778.
2. Chauhan A, Leadbitter K, Gray-Burrows KA, Vinall-Collier K, Pickles N, Baker SR, et al. An 'explosion in the mouth': The oral health experiences of autistic children. Autism. 2025;29(3):627-41. doi: 10.1177/13623613241288628.
3. Uliana JC, Del' Agnese CC, Antoniazzi RP, Kantorski KZ. Autistic individuals have worse oral status than neurotypical controls: a systematic review and meta-analysis of observational studies. Clin Oral Investig. 2024;28(2):137. doi: 10.1007/s00784-024-05500-0.
4. AlBhaisi IN, Kumar MSTS, Engapuram, A, Shafiei Z, Zakaria ASI, Mohd-Said S, et al. Effectiveness of psychological techniques in dental management for children with autism spectrum disorder: a systematic literature review. BMC Oral Health. 2022;22(1):162. doi: 10.1186/s12903-022-02200-7.
5. Godbole N, Tirupathi SP, Nair S, Afnan L, Nallapu A, Nallapu A. Effectiveness of picture-based interventions of toothbrush training on improvement of oral hygiene in children with autism spectrum disorders: A systematic review and meta-analysis. Spec Care Dentist. 2024;44(3):686-99. doi: 10.1111/scd.12950.
6. Zupin L, Sahyoun C, Krauss B, Dagri A, Rocco EM, Barbi E, et al. Effectiveness of pharmacological procedural sedation in children with autism spectrum disorder: A systematic review and meta-analysis. Acta Paediatr. 2024;113(11):2363-77. doi: 10.1111/apa.17364.
7. Yazdanbakhsh E, Bohlouli B, Patterson S, Amin M. The use of general anesthesia for dental treatment of children with special healthcare needs in Alberta, Canada. Int J Paediatr Dent. 2025;35(2):347-58. doi: 10.1111/ipd.13237.
8. Floríndez LI, Como DH, Law E, Tran CF, Johnson R, Polido JC, et al. Oral care interventions for autistic individuals: A systematic review. Autism. 2025;29(1):41-52. doi: 10.1177/13623613241260171.
9. da Motta TP, da Mota DG, Bitencourt FV, Jardim PF, Abreu LG, Zina LG, et al. Dental Caries of Individuals with Autism Spectrum Disorder (ASD): A Systematic Review and Meta-Analysis. J Autism Dev Disord. 2025. doi: 10.1007/s10803-025-06754-7. Online ahead of print.
10. Uliana JC, Del' Agnese CC, Antoniazzi RP, Kantorski KZ. Autistic individuals have worse oral status than neurotypical controls: a systematic review and meta-analysis of observational studies. Clin Oral Investig. 2024;28(2):137. doi: 10.1007/s00784-024-05500-0.
11. Stein LI, Lane CJ, Williams ME, Dawson ME, Polido JC, Cermak SA. Physiological and behavioral stress and anxiety in children with autism spectrum disorders during routine oral care. Biomed Res Int. 2014;2014:694876. doi: 10.1155/2014/694876.

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Declaration of patient consent: the authors certify that they have obtained all appropriate patient's consent forms. The photographs used in this case report were taken with the verbal consent of the children's parents.

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Exencephaly with Cervical Rachischisis, a Rare Congenital Neural Tube Malformation

Eksencefalija sa cervikalnom rahisizom - rijetka kongenitalna malformacija neuralne cijevi

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ABSTRACT

Neural tube defects (NTDs) are severe congenital anomalies arising from incomplete closure of the neural tube during embryogenesis. Among the rarest forms are exencephaly and cervical rachischisis, both of which are incompatible with life. We report a case of a 16-week gestation fetus diagnosed via ultrasound with complete absence of calvaria bones and homogeneous brain tissue consistent with exencephaly. Following legal and ethical approval, pregnancy was terminated, and examination of the fetus revealed absence of calvaria, reduction of cerebral tissue, and cervical rachischisis with exposed spinal cord. These findings are consistent with the acrania–exencephaly–anencephaly sequence. The case highlights the rapid in utero progression of neural tissue degeneration, as demonstrated by comparison of prenatal ultrasound and post-delivery findings. Discussion addresses the embryological basis, risk factors, and genetic contributions to NTDs, as well as preventive strategies emphasizing folic acid supplementation and glycemic control in high-risk pregnancies. Early detection and counseling remain critical in management of these rare and lethal anomalies.

Keywords: neural tube defect, exencephaly, anencephaly, cervical rachischisis, prenatal diagnosis

SAŽETAK

Defekti neuralne cijevi (DNC) predstavljaju teške kongenitalne anomalije nastale uslijed nepotpunog zatvaranja kranijalnog dijela neuralne cijevi tokom embriogeneze. Među najrjeđim oblicima su egzencefalija i cervikalna rahischiza, oba inkompatibilna sa životom. Prikazujemo slučaj fetusa u 16. sedmici gestacije kod kojeg je ultrazvučno dijagnosticiran potpuni nedostatak kostiju kalvarije i homogeno moždano tkivo, što je ukazivalo na egzencefaliju. Nakon dobijanja zakonskog i etičkog odobrenja, trudnoća je prekinuta, a pregled fetusa potvrdio je odsustvo kalvarije, redukciju moždanog tkiva i cervikalnu rahischizu sa izloženom kičmenom moždinom. Ovi nalazi odgovaraju akranija–eksefalis–anencefalija sekvenci. Slučaj ukazuje na brzu in utero progresiju degeneracije nervnog tkiva, što je bilo jasno vidljivo poređenjem prenatalnog ultrazvuka i postpartalnog pregleda. U diskusiji su naglašene embriološke osnove, faktori rizika i genetski doprinos nastanku NTD, kao i preventivne strategije sa naglaskom na suplementaciju folnom kiselinom i kontrolu glikemije kod rizičnih trudnoća. Rana dijagnoza i savjetovanje ostaju ključni u prevenciji ovih rijetkih i fatalnih anomalija.

Ključne riječi: defekt nuralne cijevi, eksencefalija, anencefalija, cervi kalna rahisiza, prenatalna dijagnoza

INTRODUCTION

Neural tube defects (NTD) arise when the neural tube, the embryonic precursor of the brain and spinal cord, fails to close during neurulation. The cranial region (anencephaly) or the low spine (open spina bifida; myelomeningocele) are most commonly affected.

Exencephaly is a severe congenital malformation of the neural tube, wherein the brain is not encased within the calvaria due to a defect. It is considered a precursor to anencephaly.

Anencephaly is a severe congenital malformation which is characterized by open defect of calvaria and adjacent skin, where the cranial neural tube is exposed to amniotic fluid. This severe congenital malformation is not compatible with life and nearly every live born infant survives only for a few hours.

Rachischisis is a severe neural tube defect which refers to the failure of the closure of the dorsal aspect of the vertebral foramen of many adjacent vertebrae.

Overall estimate of the prevalence, incidence and attenuation of anencephaly worldwide were 5.1 per ten thousand births (95% confidence interval 4.7-5.5 per ten thousand births), 8.3 per ten thousand births (95% confidence interval 5.5-9.9 per ten thousand births), 5.5 per ten thousand births (95% confidence interval 1.8-15 per ten thousand births) respectively the highest of which according to the subgroup analysis, belonged to the Australian continent with 8.6 per ten thousand births (95% confidence interval 7.7-9.5 per ten thousand births) (1).

CASE REPORT

A patient (G1P0) was referred to our clinic at 16 weeks pregnancy by the attending ob/gyn, due to abnormal foetal ultrasound. During an ultrasound examination at the Clinic of Gynecology and Obstetrics of the Clinical Center University of Sarajevo, complete absence of bones of the calvaria was noted. The brain matter was mostly homogenous, with normal brain structures barely recognizable (Figure 1). Prospects of continuation of the pregnancy were explained to the patient. The patient followed the legal procedure for pregnancy termination at this stage: sent her request for pregnancy termination to the CCUS Ethical Committee with all medical history relevant to this pregnancy. The request was approved given the serious malformation of the foetus which was deemed not compatible with life. The patient was informed of all the possible adverse outcomes and complications of the pregnancy termination at her gestation age. After admission at the Gynaecology Department of the CCUS, a single dose of Prepidil gel was administered intracervicaly. Around four hours later, the patient delivered a non-viable foetus at 16 weeks gestation.

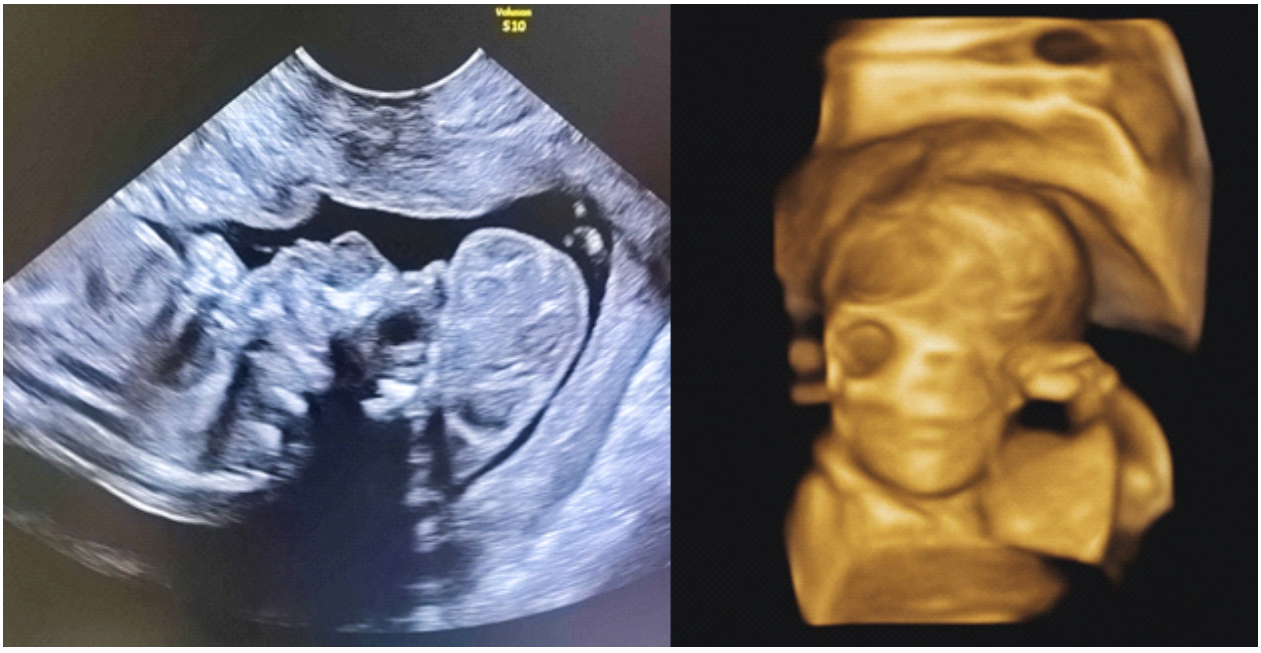

Figure 1 **Ultrasound presentation - a) sagittal view of the foetal head. Complete absence of calvaria can be noted, brain is mostly homogenous, with anatomical structures barely recognisable; b) frontal 3D ultrasound image showing the brain tissue protrudng outside of the skull.**

Once delivered, the foetus was examined: a complete absence of calvaria bones was noted, with a small clot like structure protruding from the floor of the cranial cavity (Figure 2) confirming the diagnosis of exencephaly. On further examination defect of the cervical spine was noted - cervical rachischisis, which left the cervical spinal cord exposed to the amniotic fluid. Frontal side of the foetus showed typical signs of acrania with rachischisis - absence of neck, retroflexed spine and bulbous "frog like eyes".

The patient refused any further pathological of genetical examinations of the foetus.

DISCUSSION

Neural tube defects (NTD) are serious malformations of the central nervous system that occur during embryogenesis (25 to 28 days after the conception). They are the result of abnormal neural tube closure and fusion. Neural tube is formed through the process of folding and fusion of the neural plates.

As the neural tube is being formed it also fuses in the dorso-medial line, beginning cranially and progressing caudally (2). In the case of incomplete closure and fusion of the neural tube, neural tube defects are formed. If the defect involves the embryonic structures that normally develop into the brain, anencephaly ensues. Cranial neural tubes usually occur around 25 days after the conception, and caudal around 28 days after conception.

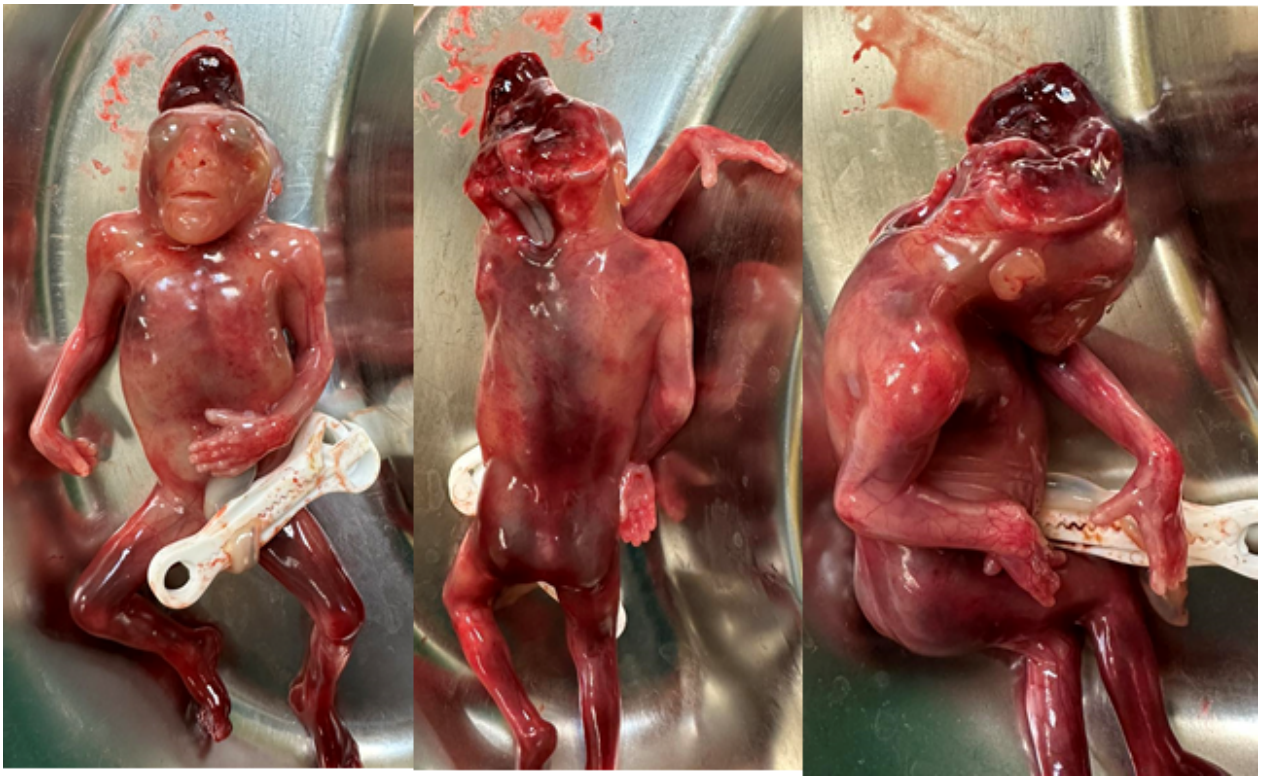

Figure 2 **Frontal (a), dorsal (b) and lateral (c) view of the foetus; a) note the absence of neck (blue arrow) and bulbous eyes (red arrow); b) note the cervical rachischisis (arrow); c) note the clot-like formation that is all that remains of the brain tissue and the reduction in its size between here and the ultrasound picture (Figure 1 a)).**

Anencephaly is a severe defect of the calvaria and brain that results from failure of the rostral neuropore to close during the fourth week. The forebrain, midbrain, and most of the hindbrain and calvaria are absent (3).

Today, the general consensus is that the anencephaly develops through acrania-exencephaly-anencephaly sequence (4). When the cranial part of neural tube fails to close development of meninges and muscles and bones of the cranium are absent (acranium) (5). As the direct consequence of the lack of these structures the brain tissue is exposed to the external factors (exencephaly), primarily amniotic fluid, inevitably causing chemical and mechanical damage. Consequently, destruction of the brain tissue occurs and anencephaly ensues. In our case it can be noted how much the volume of the brain tissue was reduced between the ultrasound examination and foetus delivery, where only 7 days had passed.

The craniofacial abnormalities in anencephaly are caused by abnormal neural induction from prosencephalic and mesencephalic neural crest tissue (6).

The acranium–exencephaly–anencephaly sequence most commonly arises from maternal folate deficiency. This deficiency may result from inadequate dietary intake of folate or from the use of medications that interfere with folate metabolism (e.g., valproate, methotrexate, trimethoprim) (7). It is well established that exposure to folate antagonists during the period of neurulation increases the risk of spina bifida, and it is reasonable to assume that the risk of anencephaly is similarly elevated.

Women with type I diabetes mellitus (DM) are at increased risk of neural tube defects (NTDs) (8). Maternal type I DM has also been associated with delayed synthesis of alpha-fetoprotein (AFP) (8,9). Measurement of maternal serum AFP concentrations is widely used as a screening tool for NTDs. When type I DM is well controlled, the risk of NTDs remains low. In contrast, gestational diabetes mellitus has not been linked to NTDs, as hyperglycaemia in these patients typically develops after the critical window for neural tube closure. Maternal hyperthermia has also been associated with an increased risk of NTDs. For this reason, pregnant women are advised to avoid hot tubs and other environments that may cause transient hyperthermia. Likewise, maternal fever during early gestation has been reported as a risk factor for both anencephaly and other NTDs (10).

Most cases of anencephaly follow a multifactorial pattern of inheritance, with interaction of multiple genes as well as environmental factors. The specific genes that are most important in NTDs have not yet been identified. Methylenetetrahydrofolate reductase (MTHFR) gene mutations are sometimes mentioned as a possible risk factor for NTDs, mostly because of how they affect the folate metabolism. Two particular mutations have been shown to carry an increased risk of NTDs; the 677C□T mutation, if homozygous increases the risk 2-4 times, the 1298A□C mutation carries lower risk (11). A second gene that might be associated with NTDs, a membrane-associated signaling complex protein called VANGL1, was described in 2007 (12).

The best way to prevent NTDs is to make sure patients are taking proper doses of folates in early pregnancy, preferably even before conception. Some countries (like the USA) mandate that rice is enriched with folic acid, which significantly reduced risk of developing NTDs (60-100% risk reduction in previous pregnancies with NTD, and 0-75% risk reduction where no previous NTD was described) (13). For women with no prior NTD history, recommended dose is 400 mcg of folic acid per day. For women with high risk, such as family history of an NTD or a prior pregnancy/birth affected by an NTD, it is recommended to increase dosage to 4000 mcg of folic acid daily starting at least one month before pregnancy.

Anencephalic neonates are not good candidates for organ transplantation because they usually don't meet the criteria for brain death, and by the time they do, their organs are no longer suitable for transplantation (14).

CONCLUSION

Neural tube defects are multifactorial foetal development malformations that nowadays rarely occur. Most of these pregnancies are terminated at early stages, as soon as the malformation is discovered. Even when these pregnancies are brought full term, these neonates rarely survive more than few hours, exceptionally a few days. In order to ensure NTD prevention for women who have pregestational diabetes mellitus we must ensure to maintain proper glucose levels thorough entire pregnancy, especially during the early weeks. Pregnant women must avoid taking any drugs that interfere with folate metabolism, and must avoid hyperthermia in early pregnancy. Sufficient folate intake is essential throughout early pregnancy, especially for patients with high risk of developing NTDs, where the dose is ten times higher than the standard recommendation, and supplementation should commence at least one month prior to conception.

REFERENCES

1. Salari N, Fatahi B, Fatahian R, Mohammadi P, Rahmani A, Darvishi N, et al. Global prevalence of congenital anencephaly: a comprehensive systematic review and meta-analysis. Reprod Health. 2022;19(1):201. doi: 10.1186/s12978-022-01509-4.
2. Greene ND, Copp AJ. Neural tube defects. Annu Rev Neurosci. 2014;37:221-42. doi: 10.1146/annurev-neuro-062012-170354.
3. Moore KL, Persaud TVN, Torchia MG. The Developing Human: Clinically Oriented Embryology. 11th ed. Edinburgh: Elsevier; 2020. SBN: 978-0-325-61155-8.
4. Wilkins-Haug L, Freedman W. Progression of exencephaly to anencephaly in the human fetus--an ultrasound perspective. Prenat Diagn. 1991;11(4):227-33. doi: 10.1002/pd.1970110404.
5. O'Rahilly M, Muller F. Human Embryology & Teratology, Wiley-Liss, Inc, New York 1992. p.253.
6. Sarnat HB, Flores-Sarnat L. Embryology of the neural crest: its inductive role in the neurocutaneous syndromes. J Child Neurol. 2005;20(8):637-43. doi: 10.1177/08830738050200080101.
7. Loungblood ME, Williamson R, Bell KN, Johnson Q, Kancherla V, Oakley GP Jr. 2012 Update on global prevention of folic acid-preventable spina bifida and anencephaly. Birth Defects Res A Clin Mol Teratol. 2013;97(10):658-63. doi: 10.1002/bdra.23166.
8. Salbaum JM, Kappen C. Neural tube defect genes and maternal diabetes during pregnancy. Birth Defects Res A Clin Mol Teratol. 2010;88(8):601-11. doi: 10.1002/bdra.20680.
9. Gabbay-Benziv R, Reece EA, Wang F, Yang P. Birth defects in pregestational diabetes: Defect range, glycemic threshold and pathogenesis. World J Diabetes. 2015;6(3):481-8. doi: 10.4239/wjd.v6.i3.481.
10. Wang M, Wang ZP, Gong R, Zhao ZT. Maternal flu or fever, medications use in the first trimester and the risk for neural tube defects: a hospital-based case-control study in China. Childs Nerv Syst. 2014;30(4):665-71. doi: 10.1007/s00381-013-2305-3.
11. Yaliwal LV, Desai RM. Methylenetetrahydrofolate reductase mutations, a genetic cause for familial recurrent neural tube defects. Indian J Hum Genet. 2012;18(1):122-4. doi: 10.4103/0971-6866.96680.
12. Kibar Z, Torban E, McDearmid JR, Reynolds A, Berghout J, Mathieu M, et al. Mutations in VANGL1 associated with neural-tube defects. N Engl J Med. 2007;356(14):1432-7. doi: 10.1056/NEJMoa060651.
13. Murphy ME, Westmark CJ. Folic Acid Fortification and Neural Tube Defect Risk: Analysis of the Food Fortification Initiative Dataset. Nutrients. 2020;12(1):247. doi: 10.3390/nu12010247.
14. Use of anencephalic newborns as organ donors. Paediatr Child Health. 2005;10(6):335-7. PMID: 19675842; PMCID: PMC2722973.

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