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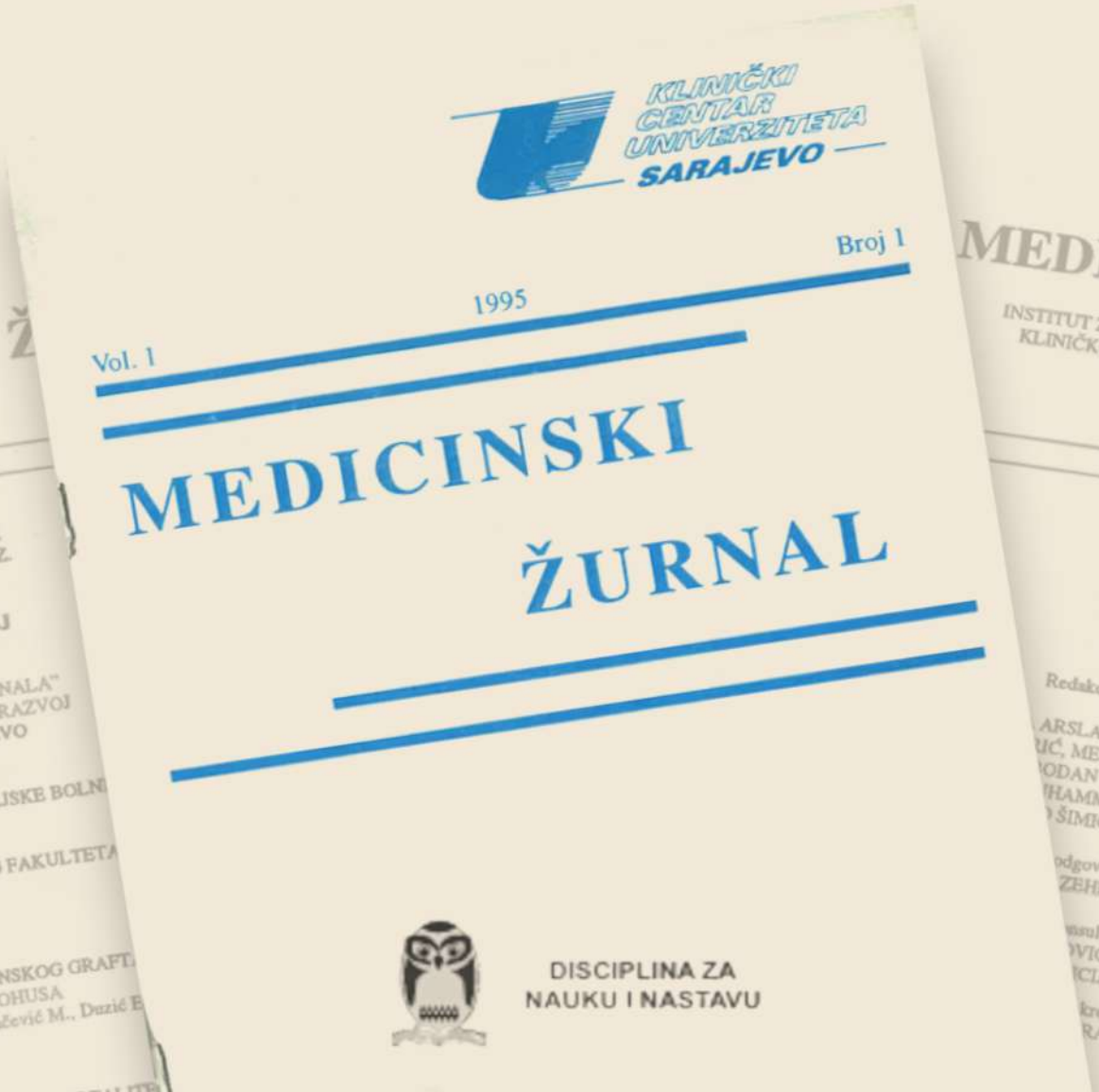
A tribute to the Vol. 1 from 1995



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The Medical Journal is the official quarterly journal of the Discipline for Research and Development of the Clinical Center University of Sarajevo and has been published regularly since 1994. It is published in the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Croatian and Serbian as well as in English.

The Medical Journal aims to publish the highest quality materials, both clinical and scientific, on all aspects of clinical medicine. It offers the reader a collection of contemporary, original, peer-reviewed papers, professional articles, review articles, editorials, along with special articles and case reports.

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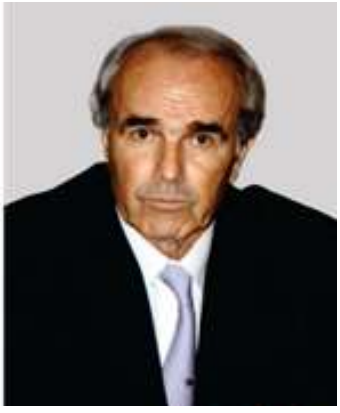
Medical Journal of the CCUS: Three Decades of Growth and Development

The Medical Journal, a general medical journal publishing all types of articles in the field of biomedical science and healthcare, is published by the Discipline for Research and Development (Institute for Scientific Research and Development) of the Clinical Center University of Sarajevo. The Institute in which the complete professional, scientific and teaching potential of the Clinical Center is functionally sublimated was established on 23 April 1993 as a necessity of the CCUS, especially since the CCUS has become an equal member of the Sarajevo University. On the professional level, the Institute has the task to ensure and improve the professional development of both individuals and organizational units, while on the educational level the Institute's task is to ensure and improve quality theoretical and practical teaching. The first director of the Institute was Prof. Dr. Faruk Konjhodžić, who functionally established the Institute in 1993. By decision of the Government of the Republic of Bosnia and Herzegovina, Prof. Dr. Fuad Šišić was appointed Director of the Institute on 13 November 1993, and remained in office until May 2004, when he retired. Through the efforts of Prof. Dr Šišić, in February 1999 the Institute moved into a reconstructed building where the Central Library with a collection of over 5,100 books and 326 magazines was established along with the Department for Visual Communications and Informatics, and the Publications Department. Professor Šišić's successors, who made a significant contribution to the work and activities of the Institute, were Prof. Dr. Ismet Gavrankapetanović, Prof. Dr. Damir Aganović, Prof. Dr. Lilijana Oruč, Prof. Dr. Zoran Hadžiahmetović, Prof. Dr. Enra Suljić-Mehmedika. Currently, the acting Director of the Institute is Prof. Dr. Sanko Pandur, appointed to that position in 2024.

Prof.dr. Faruk Konjhodžić



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Prof. dr. Enra Mehmedika-Suljić

Prim. dr. sci. Sanko Pandur

The first printed issue of the Medical Journal was published in 1995, containing three introductory articles, two scientific papers, one professional paper, five preliminary reports, one educational article, one case study, a historical article, as well as reports, news, library news and a review of books and magazines. The first wartime issue was published on the 100th anniversary of the existence and operation of the National Hospital, today's Clinical Center, and the 50th anniversary of the Faculty of Medicine in Sarajevo. The first Publishing Editor of the Medical Journal was Prof. Dr. Zehra Dizdarević, who remained in that position until 2006, followed by Prof. Dr. Mirza Dilić and Prof. Dr. Damir Aganović. The current Publishing Editor of the Medical Journal is Prof. Dr. Refet Gojak.

Prof. dr Zehra Dizdarević

Prof. dr Mirza Dilić

Prof.dr. Damir Aganović

Prof. dr Refet Gojak

In 2004, the Journal changed its design and format (the Journal got a website within the CCUS), with a significant improvement in quality, and since 2005 the frequency of publication changed from twice a year to four times a year. The journal received a CIP and ISSN number in its initial publication. There has been professional exchange of the Journal with medical journals from the neighboring countries (Slovenia, Croatia, Serbia and Montenegro), thus ensuring a part of the periodical publications supply. Since 2008 the Journal has been represented in several EBSCO collections (Academic Search Complete, Academic Search Ultimate, Central & Eastern European Academic Source, STM Source).

1995

2010

2025

The Evolution of the Medical Journal of the Discipline for Research and Development of the Clinical Center University of Sarajevo.

During the thirty-year publication period, the journal's editorial office, the Discipline for Research and Development, the CCUS, as well as the authors of the papers, have been striving to improve the quality of the Journal, in terms of the content, specifically semantic- informational value of the published articles, and their technical-methodological aspects, keeping track of the innovations, requirements and standards of modern information and communication technologies. Meeting the high requirements of the relevant indexed databases (MEDLINE, Scopus, Copernicus, etc.) requires a high quality of publications, and we will continue to work on improving the quality of the Journal in order that it is soon registered in one of the globally recognized medical databases.

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Medical Journal of the Discipline for Research and Development
Clinical Center University of Sarajevo

Association Between Left Main Coronary Artery Stenosis and Peripheral Arterial Disease: A Prospective Comparative Study

Povezanost stenoze glavnog stabla lijeve koronarne arterije i periferne arterijske bolesti: prospektivna komparativna studija

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ABSTRACT

Introduction: coronary artery disease (CAD) and peripheral arterial disease (PAD) frequently coexist as manifestations of systemic atherosclerosis, sharing common risk factors and pathophysiological mechanisms. The presence of PAD in patients with CAD is associated with higher morbidity and mortality, particularly when the left main (LM) coronary artery is affected. Identifying the relationship between LM stenosis and extracardiac vascular involvement is essential for comprehensive cardiovascular risk assessment and perioperative management. Aim: to compare general and periprocedural outcomes among defined groups of patients and to correlate the association between coronary artery disease and peripheral artery disease. Materials and methods: we assessed 120 patients (60 of whom had left main stenosis (LM stenosis) and 60 without left main stenosis but with significant coronary artery disease and an indication for surgery). We defined general risk factors and perioperative risks among groups. The study was a clinical, prospective, descriptive-analytical study. The results were processed by descriptive group statistics, with the determination of statistical significance of differences between groups up to the level of $\alpha = 0.05$. Parametric data were tested by the Student T test, the Chi-square test, and comparisons between the groups were verified through correlation tests. Results: a statistically significant difference was found in the age of the patients between the two groups (p=0.0377), while no statistically significant difference in the distribution of patients by gender, and the presence of risk factors like arterial hypertension, diabetes mellitus, obesity, and tobacco consumption was found between the groups. The results showed a significant difference in the distribution of patients with extracardiac vasculopathies between groups, and a higher incidence of peripheral vascular disease in the group of patients with left main stenosis was found (p=0.0372). Conclusion: given the significant difference in the prevalence of extracardiac vasculopathies between the two compared groups, patients who have been diagnosed with advanced peripheral artery disease should undergo coronary angiography for the assessment of possible coronary artery disease, in search particularly for LM stenosis and vice versa.

Keywords: left main coronary artery stenosis, peripheral arterial disease, coronary artery disease, atherosclerosis

SAŽETAK

Uvod: koronarna arterijska bolest (KAB) i periferna arterijska bolest (PAB) često koegzistiraju kao manifestacije sistemske ateroskleroze, dijeleći zajedničke faktore rizika i patofiziološke mehanizme. Prisustvo PAB kod pacijenata s KAB povezano je s većim morbiditetom i mortalitetom, naročito kada je zahvaćeno glavno stablo lijeve koronarne arterije (GS LKA). Prepoznavanje odnosa između stenoze GS LKA i ekstrakardijalnog vaskularnog zahvata ključno je za sveobuhvatnu procjenu kardiovaskularnog rizika i perioperativno upravljanje. Cilj: uporediti opće i periproceduralne ishode među definisanim grupama pacijenata te analizirati povezanost između koronarne arterijske bolesti i periferne arterijske bolesti. Materijali i metode: u istraživanje je uključeno 120 pacijenata, od čega je 60 imalo stenozu glavnog stabla lijeve koronarne arterije, a 60 nije imalo stenozu glavnog stabla, ali su imali značajnu koronarnu arterijsku bolest s indikacijom za operativno liječenje. Definisani su opći faktori rizika i periproceduralni rizici među grupama. Istraživanje je bilo kliničko, prospektivno, deskriptivno-analitičko. Rezultati su obrađeni deskriptivnom statistikom grupa, uz utvrđivanje statističke značajnosti razlika između grupa na nivou $\alpha = 0,05$. Parametarski podaci testirani su Studentovim T-testom i hi-kvadrat testom, a poređenja između grupa potvrđena su testovima korelacije. Rezultati: utvrđena je statistički značajna razlika u dobi pacijenata između dvije grupe (p=0,0377), dok nije bilo značajne razlike u distribuciji pacijenata prema spolu niti prisustvu faktora rizika poput arterijske hipertenzije, dijabetesa melitusa, gojaznosti i pušenja. Rezultati su pokazali značajnu razliku u distribuciji pacijenata s ekstrakardijalnim vaskulopatijama između grupa, s većom učestalošću periferne vaskularne bolesti u grupi pacijenata sa stenozom glavnog stabla lijeve koronarne arterije (p=0,0372). Zaključak: s obzirom na značajnu razliku u prevalenci ekstrakardijalnih vaskulopatija između dvije posmatrane grupe, pacijenti kod kojih je dijagnosticirana uznapredovala periferna arterijska bolest trebaju biti podvrgnuti koronarnoj angiografiji radi procjene moguće koronarne arterijske bolesti, posebno stenoze glavnog stabla lijeve koronarne arterije, i obrnuto.

Ključne riječi: stenoza glavnog stabla lijeve koronarne arterije, periferna arterijska bolest, koronarna arterijska bolest, ateroskleroza

INTRODUCTION

Coronary heart disease (CHD) accounts for approximately one-third to one-half of the total cases of cardiovascular disease (CVD). The lifetime risk of CHD was illustrated in the Framingham Heart Study of 7733 participants, ages 40 to 94, who were initially free of CHD (1). The lifetime risk for individuals at age 40 was 49% in males and 32% females. Even those who were free from CHD at age 70 had a non-trivial lifetime risk of developing CHD (35 and 24% in males and females, respectively). CVD and its related complications remain highly prevalent and expensive to treat . CVD is the leading cause of death in most developed countries, with approximately one million Americans dying annually from CVD .The prevalence of CVD is rapidly increasing in resource-limited countries as well.

Many risk factors for CVD are modifiable by specific preventive measures. In the worldwide INTERHEART study of patients from 52 countries, nine potentially modifiable factors accounted for over 90 percent of the population-attributable risk of a first MI: smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, lack of daily consumption of fruits and vegetables, regular alcohol consumption, and lack of regular physical activity . Most patients with CVD have at least one established or borderline risk factor other than age and sex —. However, it is clear that there are other risk factors, some of which are not all treatable, that may also be important. The additive value of screening for these risk factors has not been firmly established, and there is only limited evidence that targeted therapeutic intervention will reduce the risk associated with these factors .

Imaging studies and other specialized tests often detect evidence of atherosclerosis in arteries, with typical findings including increased arterial thickness, stiffness, and calcification. Such findings provide evidence of subclinical atherosclerosis that may progress to clinical CVD affecting specific arterial pools. Such findings are subclinical phases in the progression of atherosclerotic disease that are often associated with the risk of future clinical atherosclerotic CVD events.

Significant PVD is defined by the presence of at least 50% stenosis. Examples of such findings include: arterial intima-media thickness Carotid artery intima-media thickness (IMT) is linked to the atherosclerotic process because of its association with known cardiovascular risk factors –. Arterial stiffness - Arterial stiffness, measured as the aortic pulse wave velocity (PWV) between the carotid and femoral arteries, is a predictor of cardiovascular events . Arterial calcification - Calcium deposits in extracoronary arteries, particularly the aortic arch and abdominal aorta, may be a marker for CVD and an increase in cardiovascular events and overall mortality . Aortic arch - Calcification of the aortic arch is associated with a greater risk of CVD and total mortality.

MATERIALS AND METHODS

The research was clinical, prospective, descriptive-analytical, and manipulative. The results are displayed in the tables. General risks among defined groups were investigated according to anamnestic information, medical history, clinical examination, and laboratory findings. The definition of periprocedural risks was made based on results of clinical and laboratory findings, echocardiography, and color Doppler assessment of carotid and iliacofemoral pools. The duration of hospitalization and patients' outcomes were monitored on the basis of standard medical documentation.

The results were processed by descriptive group statistics with the determination of statistical significance of differences between the observed groups up to the level of $\alpha = 0.05$. Parametric data were tested by the Student T test, the Chi-square test, and comparisons between the groups were verified through correlation tests.

RESULTS

The study included 120 patients, of which 60 subjects had left main stenosis (Group 1 - G1) and 60 elective subjects (Group 2 - G2) who did not require urgent operative treatment

Table 1 **Demographic and clinical characteristics of patients in Group 1 and Group 2.**

Parameter	Group 1 (G1, n=60)	Group 2 (G2, n=60)	All patients (N=120)	p-value / Test
Age (years)	61.6 ± 9.0 (36–80)	58.0 ± 9.3 (31–77)	59.8 ± 9.3 (31–80)	p*=0.038
Gender	M: 46 (77%); F: 14 (23%)	M: 52 (87%); F: 8 (13%)	M: 98 (82%); F: 22 (18%)	p**=0.238
Hypertension	56 (93%)	58 (97%)	114 (95%)	p=0.657
Diabetes mellitus	17 (28%)	19 (32%)	36 (30%)	p**=0.842
Obesity	25 (42%)	20 (33%)	45 (37.5%)	p**=0.451
Smoking	40 (67%)	41 (68%)	81 (67.5%)	p**=1.000
History of ICV	2 (3%)	3 (5%)	6 (5%)	p**=1.000
Extracardiac vasculopathies	28 (47%)	16 (27%)	44 (36.7%)	p**=0.037

*t test;
**χ^2 test
Values are presented as mean ± SD or number (%). p-values were calculated using the t-test or chi-square test as appropriate.
NS = not significant; ICV = ischemic cerebrovascular event.

Patients in Group I were significantly older than those in Group 2 (61.6 ± 9.0 vs. 58.0 ± 9.3 years, p=0.038). The overall sample was predominantly male (82%), with no significant difference between groups (p=0.238). The frequency of hypertension, diabetes mellitus, obesity, smoking, and prior ischemic cerebrovascular events did not differ significantly between groups (all p>0.45).

The analysis performed through the chi-squared independence test showed a significant difference in the distribution of patients with extracardiac vasculopathies between groups, x2 (1, n=120) = 4.342, p = 0.0372.

Definition of angiographic features

Angiographic characteristics of LMA segments in Group I Fisher's exact tests did not show a statistically significant difference between angiographic features on LMA segments in group I (Table 2).

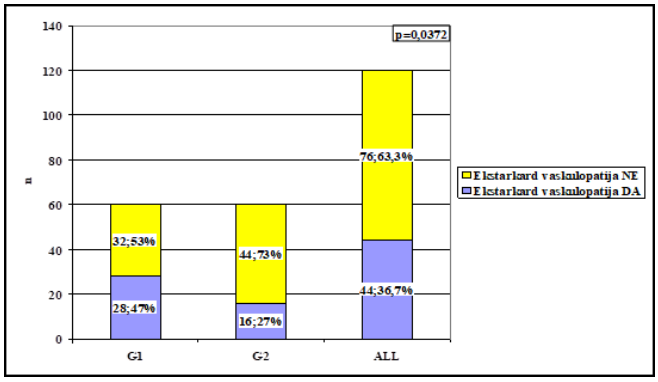

Figure I **Frequency distribution of subjects with extracardiac vasculopathies by groups.**

Table 2 **Angiographic characteristics of LMA in Group I.**

	5a proximal LM			5b medium LM			5c distal LM		
	Occlusion	Subocclusion	Stenosis	Occlusion	Subocclusion	Stenosis	Occluss ion	Subocclusion	Stenosis
GI	0	4	4	0	I	I	0	II	40
	p>0,05			p>0,05			p>0,05		

DISCUSSION

From February 2024, new guidelines from the European Association for Cardio-Thoracic Surgery (EACTS) and the Society of Thoracic Surgeons (STS) have, for the first time, recognized the aorta as "an organ in its own right". Accordingly, five large vascular pools have been defined, each of which must be evaluated. The coronary pool is of primary interest in revascularization in cardiac surgery, but the aorta as an organ, the carotid, renovascular pool, and peripheral arterial pool need to be assessed preoperatively, and if LM stenosis represents an emergency, they should be investigated postoperatively.

In our study, a statistically significant difference was found in the age of the patients between the two groups (p=0.0377), while there was no statistically significant difference in the distribution of patients by gender, and the presence of risk factors like arterial hypertension, diabetes mellitus, obesity, and tobacco consumption. The results showed a significant difference in the distribution of patients with extracardiac vasculopathies between the groups (p=0.0372).

Analyzing the presence of peripheral vascular disease (PVD) in our study as part of regular preoperative preparation, it was found that significant PVD was represented in 36.66% of patients. There was a significant difference between the two compared groups, given that PVD in Group I (patients with LM stenosis) was found in 28 patients or 46.66%, while in Group 2 (i.e., elective patients), the prevalence of peripheral vascular disease was found in 16 patients or 26.66%. According to the protocol of our institution, the study used Doppler echo to assess the carotid and iliacofemoral segments.

The high prevalence of combined coronary and peripheral vascular disease was confirmed in two large international studies, REACH (Reduction in Atherothrombosis for Continued Health) and AGATHA (AG Atherothrombosis Assessment), where 26 to 30% of patients had polyvascular disease. In 60% of patients with severe PVD who required surgery, a significant lesion on at least one coronary artery was found. The presence of combined PVD and CAD doubles the mortality rate at the level of 4.6% per year compared to the isolated disease of a single vascular pool. Severe PVD seems to be a much more important predictor of mortality and worsening prognosis than preoperative acute myocardial infarction (AMI) or pronounced angina (13).

CAD and PVD represent a highly prevalent combination in today's population due to the aging and risk factors for the development of atherosclerotic disease. Cooperation between a vascular and a cardiac surgeon can sometimes be unavoidable, and the assessment of vascular condition is necessary in preoperative preparation for CABG. Peripheral vascular disease is often subclinical, but may be associated with calcified, incompressible peripheral arteries, which are a poor predictor of coronary disease(14).

In conclusion, we can say that the treatment of patients with combined coronary artery disease and peripheral vascular disease is extremely complex. Early diagnosis and secondary prevention are essential to reduce the risk, and the identification and treatment of comorbidities can contribute to a better perspective for these patients.

Patients who have been diagnosed with advanced peripheral artery disease must undergo CT coronary angiography for the assessment of eventual coronary artery disease, particularly LM stenosis. On the other hand, patients with LM disease must be carefully investigated for signs of stenotic and obstructive PAD and aortic pathology. Close cooperation between internists, cardiologists, angiologists, radiologists, vascular surgeons, anesthesiologists, and cardiac surgeons is the key to success in the treatment of these patients.

CONCLUSION

Stenosis of the main stem of the left coronary artery has been defined as an independent predictor of cardiovascular risk for sudden cardiac death and mortality in cardiology and cardiac surgery. The higher incidence of peripheral vascular disease in the group of patients with LM stenosis indicates the need for diagnostic assessment of coronary arteries in patients with previously diagnoses peripheral vascular disease and on the other side patients with diagnoses LM disease must be carefully investigated for signs of stenotic and obstructive PAD and aortic pathology. Future multicenter studies with larger cohorts and comprehensive vascular imaging are warranted to confirm these associations and refine diagnostic protocols.

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Analysis of Microvascular Blood Vessel Density and Surface Fractions for Markers CD34 and CD105 as Predictors of Pleural Invasion in Non-Small Cell Lung Cancer

Analiza mikrovaskularne gustine krvnih sudova i površinskih frakcija za markere CD34 i CD105 kao prediktora za javljanje pleuralne invazije kod nemikrocelularnog karcinoma pluća

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ABSTRACT

Introduction: the growth of every cancer requires neovascularization, an essential process in the progression and metastasis of malignant tumors, which severely influences the treatment and survival in patients with non-small cell lung cancer (NSCLC). CD34 and CD105 expression exhibit remarkably high specificity for newly developing neoplastic vessels, making it an important indicator of angiogenesis. Pleural invasion is a known adverse prognostic factor in NSCLC.Aim: to determine whether the microvascular density and surface fraction for CD34 (MVDC34 and AFCD34) and CD105 (MVD105 and AFCD105) could predict the occurrence of pleural invasion. Materials and methods: the study included 120 patients with NSCLC, who underwent one of the anatomic resection procedures on the lungs with histopathological examination according to the TNM classification, where MVDC34, AFCD34, MVD105, and AFCD105 were analyzed concerning the occurrence of pleural invasion in patients with NSCLC. Result: almost a third of our patients with NSCLC had a histopathologically verified pleural invasion. MVDCD34 is a good predictor of pleural infiltration in patients with NSCLC, with a 1.14 times higher probability of higher values of MVDCD34 in patients without pleural invasion. Conclusion: MVDCD34 is a strong predictor of pleural invasion and can be used as a beneficial biomarker in the therapy of patients with NSCLC.

Keywords: CD34 antigen, CD 105 antigen, microvascular density, pleura, mon-small cell lung cancer

SAŽETAK

Uvod: rast svakog karcinoma zahtijeva neovaskularizaciju, bitan proces u progresiji i metastaziranju zloćudnih tumora, što ozbiljno utječe na liječenje i preživljavanje pacijenata sa mikrocelularnim karcinomom pluća (NSCLC). Ekspresija CD34 i CD105 pokazuje veoma visoku specifičnost za novorazvijene neoplastične žile, što je čini važnim pokazateljem angiogeneze. Pleuralna invazija je poznati nepovoljan prognostički faktor kod pacijentaa sa NSCLC. Cilj: utvrditi mogu li mikrovaskularna gustoća i površinska frakcija za CD34 (MVDC34 i AFCD34) i CD105 (MVD105 i AFCD105) predvidjeti pojavu pleuralne invazije kod pacijenata sa NSCLC. Materijali i metode: u istraživanje je uključeno 120 pacijenata sa NSCLC-om, kod kojih je učinjena anatomska resekcija i patohistološka verifikacija tumora prema TNM klasifikaciji, gdje su MVDC34, AFCD34, MVD105 i AFCD105 analizirani u relaciji sa pojavom pleuralne invazije kod pacijenata sa NSCLC-om. Rezultat: gotovo trećina naših pacijenata sa NSCLC imala je histopatološki potvrđenu pleuralnu invaziju. MVDCD34 je dobar prediktor pleuralne invazije, sa 1,14 puta većom vjerojatnošću viših vrijednosti MVDCD34 kod pacijenata bez pleuralne invazije. Zaključak: MVDCD34 je snažan prediktor pleuralne invazije i može se koristiti kao koristan biomarker u terapiji pacijenata sa NSCLC.

Ključne riječi: CD 34 antigen, CD105 antigen, mikrovaskularna gustina, pleura, nemikrocelularni karcinom pluća

INTRODUCTION

Tumor angiogenesis, expressed as intratumoral microvascual blood vessel density (MVD), and quantified using specific antibodies against endothelial cells (Endothelial cells - EC), is closely related to tumor growth and postoperative prognosis of patients with non-small cell lung cancer (NSCLC). The anti-EC antibody that binds to the CD34 protein (transmembrane phosphoglycoprotein) on the cell surface functions as an adhesion factor on cells. CD105 (a homodimeric membrane glycoprotein) expressed on ECs can bind transforming growth factor β1 and transforming growth factor β (1). Unlike pan-EC antibodies such as CD34, antibodies to CD105 can preferentially react with ECs of all angiogenic tissues, including tumors, but weakly or not at all with those of most normal tissues, which may suggest the superiority of CD105 as a marker of angiogenesis in clinical studies (2).

Invasion of the visceral pleura (IVP) is recognized as a negative prognostic factor in patients with NSCLC, whereas the presence of IVP alone increases the "T" descriptor from T1 to T2. This is important because adjuvant chemotherapy is sometimes considered for patients after complete resection for stage IB NSCLC, but is not a valuable resource for stage IA NSCLC patients (3,4).

Moreover, NSCLC that invaded the elastic layer of the visceral pleura demonstrated a worse prognosis and was characterized by strong growth and aggressive invasion (5). Regarding the TNM classification by the pleural involvement, all NSCLC are divided into the following categories: PL0 - tumor without invasion of any layer of the visceral pleura; PL1 - tumor invades the elastic layer of the visceral pleura but does not penetrate the surface of the visceral pleura; PL2 - tumor invades the surface of the visceral pleura through all layers; PL3 - tumor invades the parietal pleura. Patients with PL2 have significantly worse postoperative survival outcomes than those with PL1, with the percentage of pleural recurrence being significantly higher in PL2 than in the PL1 group.

AIM

The aim of this study was to determine whether the microvas cular density and surface fraction for CD34 (MVDC34 and AFCD34) and CD105 (MVD105 and AFCD105) could be beneficial in predicting the occurrence of pleural invasion in patients with NSCLC.

MATERIALS AND METHODS

This cross-sectional, observational study was conducted at the Clinic of Thoracic Surgery of the Clinical Center University of Sarajevo (tissue sampling) and the Department for Pathological-Anatomical and Molecular Diagnostics of the Joint Medical Service of the Institute for Pulmonary Diseases of Vojvodina - Sremska Kamenica (histopathological and immunological staining and testing), and it included 120 adult patients with NSCLC, who underwent anatomic lung resection during one-year period, specifically in the period from 1 June 2016 to 1 June 2017.

An accurate histopathological diagnosis according to the TNM classification system (UICC and AJCC in 2016) was determined. In all 120 subjects, additional histopathological staining with antibodies/markers for CD34 and CD105 was performed, which enabled the determination of the intensity of their expression along with the determination of the microvascular density of blood vessels - MVDCD34 and MVDCD105 and the surface fraction of both mentioned markers - AFCD34 and AFCD105, with the help of an add-on called Analyze Particles.

Three areas with the most positive blood vessels were identified, which were called 'hot spots'. From each 'hot spot' area, three photos were taken with 200x magnification, and blood vessels were counted within one field of view. Fiji software with the addition of Cell Counter was used for cell counting. Any endothelial cell or cluster of endothelial cells that were diaminobenzidine (DAB) positive and separated from adjacent blood vessels, tumor cells, and other connective tissue elements were considered structures that could be included in the final pool of blood vessels. Within the Analyze particles function for black and white photos, based on the contrast created by DAB chromogen, the surface fraction, i.e. the percentage of the region of interest on the photo that is stained with a chromogen (AFCD34,AFCD105) was thoroughly analyzed.

Descriptive statistical methods used measures of central tendency (Arithmetic mean), measures of variability (Standard deviation), and relative numbers (Structure indicators). χ^2 test, Fisher's exact test, Mann-Whitney U test, and Kruskal-Wallis test as non-parametric statistical analysis methods were also used. Binary and multinominal logistic regression analysis was performed to analyze the predictive ability of morphometric parameters. The correlation between the morphometric parameters for the CD34 and CD105 markers was examined using the Pearson correlation coefficient. Fisher's exact test and χ^2 test were considered statistically significant when p values were less than 0.05.

RESULTS

Among 120 patients included in this study, 78 (65%) were male, and 42 (35%) were female patients. The average age was 62.53± 5.4 years. The subjects were divided into four age groups (55-59, 60-64, 65-69, and 70-74 years - the youngest patient was 55 and the oldest was 74).

Adenocarcinoma was found in 53.3% (64) of patients, whereas squamous cell carcinoma was histopathologically verified in the remaining 46.7% (56) of patients. We did not verify other types of NSCLC among patients in our study. Lobectomy was the modality of choice in 82 patients, i.e. 68.3% of all cases. Pneumonectomy was performed in 26 (21.7%) patients and bilobectomy in the remaining 12 (10%) patients.

Vascular invasion was found in 27.3% (30) of patients. Analyzing the relationship between the two different types of NSCLC found in this study (adenocarcinoma and squamous cell carcinoma), no correlation was found between the type of tumor and the presence of vascular invasion (Fisher's test=0.02; p = 0.99).

Descriptive statistical data of values of MVDCD34, MVDCD 105,AFCD34, and AFCD105 is demonstrated in Table 1.

Table 1 **Descriptive statistics of microvascular blood vessel density and surface fraction of histopathological preparations stained for CD34 and CD105 markers.**

MVDCD34	Mean value	28.58
	Median	26.30
	Standard deviation	11.06
	Minimum	0.61
	Maximum	62.30
AFCD34	Mean value	3.36
	Median	3.08
	Standard deviation	2.05
	Minimum	0.66
	Maximum	11.62
MVDCD105	Mean value	14.60
	Median	15.80
	Standard deviation	6.21
	Minimum	0.18
	Maximum	29.50
AFCD105 (%)	Mean value	1.99
	Median	1.63
	Standarddeviation	1.77
	Minimum	0.08
	Maximum	10.32

The MVDCD34 is statistically significantly different in patients with and without pleural invasion, i.e. patients with no pleural invasion had a lower MVD. The AFCD34 marker is not statistically significantly different between patients with and without pleural invasion. The remaining MVD and AF values for the CD105 marker did not show statistically significant differences between patients with and without pleural invasion, as demonstrated in Table 2.

Table 2 **Mann-Whitney analysis of MVDCD34, MVDCD105, AFCD34, and AFCD105 in patients with and without pleural invasion (n =120).**

	Yes	No	U / z	P
MVDVD34	21	29.20	664 / -3.59	< 0.001 *
AFCD34 (%)	2.65	3.19	1032 / -1.13	0.26
MVDCD105	15.20	16.45	1044 / -1.05	0.29
AFCD105 (%)	1.63	1.56	1172 / -0.19	0.85

*statistically significant difference

Analyzing the relationship between different types of NSCLC and the presence of pleural invasion, no significant statistical significance was found (Fisher's test = 1.58; p = 0.28) (Table 3).

Table 3 **Correlation of different types of NSCLC with the presence or absence of pleural invasion.**

	Yes	No	p
Adenocarcinoma	14 (12.7%)	48 (43.6%)	0.28
Squamous cell carcinoma	16 (14.5%)	32 (29.1%)	

Binary logistic regression showed that MVDCD34 is a good predictor (p=0.003) for pleural invasion in NSCLC. There is a 1.14 times higher probability of higher MVDCD34 values in patients without pleural invasion than those with. Other morphometric parameters, vascularization, and neovascularization, did not prove to be good predictors and have no statistically significant association with the occurrence of pleural invasion in NSCLC (Table 4).

Table 4 **MVDCD34, MVDCD105, AFCD34, and AFCD105 as predictors for pleural invasion in NSCLC.**

Morphometric parameters	Pleural invasion absent OR(95% CI)	P
MVDCD34	1.14 (1.051.24)	0.003*
AFCD34 (%)	0.66 (0.411.05)	0.08
MVDCD105	0.95 (0.851.05)	0.31
AFCD105 (%)	1.17 (0.521.20)	0.49

Reference category: pleural invasion present

DISCUSSION

Among 120 patients enrolled in this cross-sectional study, pleural invasion was histopathologically verified in 30 (27.3%) patients. Observing the possible correlation between different types of NSCLC and the presence of pleural invasion, no statistically significant difference was found (Fisher's test = 1.58; p = 0.28) between patients with adenocarcinoma and squamous cell carcinoma with pleural invasion.

The invasion of the visceral pleura is considered one of the most important prognostic factors in patients undergoing surgery for NSCLC (6,7) and is included in the TNM classification as a factor that changes the 'T' descriptor from T1 to T2 (8). According to the study of Osaki T, et al., who analyzed the survival of 474 patients with T1 and T2 NSCLC to assess the impact of visceral pleural invasion, the latter was found in 27.7% of patients, which is almost identical to the results of our study (9).

In the study of Seok Y, et al., adenocarcinoma was the most common histological type of NSCLC in patients with pleural invasion (65.8%), similar to our study, whereas squamous cell carcinoma was present in 32.1% of patients. Other types of NSCLC were only present in 2.1% of patients (10). The authors of this study stated that their results correspond with the majority of earlier studies where the ratio of the number of patients with visceral pleural invasion between those with adenocarcinoma and those with squamous cell carcinoma varied, but adenocarcinoma was always more prevalent.

Patients with no pleural invasion had a statistically significantly different (lower) MVDCD34 compared to those with. The AFCD34 is not statistically significantly different between patients with and without pleural invasion. The same examination of MVDCD105 and AFCD105 values did not show statistically significant differences between these two groups of patients.

Last but not least, MVDCD34 has shown to be a good predictor for the occurrence of pleural invasion in NSCLC, more precisely, there is a 1.14 times greater probability that higher MVDCD34 values will occur in pedtients without compared to patients with pleural invasion.

CONCLUSION

Pleural invasion occurs predominantly in patients with adenocarcinoma, overall in almost a third of all patients included in our study. Patients without pleural invasion have statistically significantly lower values of MVDCD34, i.e. there is a 1.14 times greater probability that higher MVDCD34 values will be found in patients without pleural infiltration, making it a beneficial biomarker for the prognosis of pleural invasion in patients with NSCLC.

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Importance of Electronic Health Records for Emergency Department Timelines of Care in Interhospital Transfers

Značaj elektronskih zdravstvenih kartona za operativnu efikasnost hitnih odjeljenja u međubolničkim transferima

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ABSTRACT

Introduction: transfers of critically ill patients from secondary healthcare facilities to the emergency department (ED) of tertiary care centers are often associated with an increased ED length of stay (LOS) and may contribute to additional adverse clinical outcomes. Aim: to determine whether the use of electronic health records (EHRs) can reduce emergency department length of stay (ED LOS) and improve operational efficiency during the transfer process. Materials and methods: data on 137 interhospital transfers (IHTs) of adult patients from six secondary level healthcare hospitals admitted to the ED of a tertiary clinical center between 1 December 2024 and 28 February 2025, were retrospectively analyzed. Patients were grouped based on the presence or absence of EHRs. Various data were recorded. The ED LOS was measured as the outcome of ED timeliness of care. Results: patients with EHRs had a significantly shorter ED LOS compared to those without EHR. The non-EHR group underwent more frequent diagnostics and consultations, suggesting a delayed decision-making process. Regression analysis identified EHR use as a significant predictor of reduced ED LOS while diagnostics and intensive care unit (ICU) admissions were associated with prolonged LOS. Conclusion: the findings of this study demonstrate that IHTs with EHR-supported transitions are associated with a significantly shorter LOS in the ED compared to transfers without EHR support. These findings support the implementation of electronic health records as a strategy to optimize emergency department timeliness and efficiency in interhospital transfers.

Keywords: electronic health records, timeliness of care, interhospital transfers

SAŽETAK

Uvod: premještaji kritično oboljelih pacijenta iz ustanova sekundarnog nivoa zdravstvene njege u hitne odjele tercijarnih kliničkih centara često su povezani sa produženim boravkom u urgentnom centru što može doprinijeti dodatnim nepovoljnim kliničkim ishodima. Cilj: utvrditi da li upotreba elektronskog zdravstvenog kartona, može skratiti dužinu boravka na hitnom odjeljenju i unaprijediti operativnu efikasnost tokom procesa međubolničkih transfera. Materijali i metode: retrospektivno su analizirani podaci o 137 međubolničkih transfera odraslih pacijenata iz šest bolnica sekundarnog nivoa zdravstvene njege primljenih na hitno odjeljenje tercijarnog kliničkog centra u periodu od 1. decembra 2024. do 28. februara, 2025. godine. Pacijenti su grupisani na osnovu prisustva ili odsustva elektronskog zdravstvenog kartona. Zabilježeni su različiti podaci. Dužina boravka u hitnom odjeljenju je izmjerena kao ishod pravovremenosti pružanja njege. Rezultati: pacijenti sa elektronskim zdravstvenim kartonom su imali značajno kraći boravak na hitnom odjeljenju u poređenju sa pacijentima koji nisu imali elektronski zdravstveni karton. Grupa bez elektronskog zdravstvenog kartona češće je bila podvrgnuta dijagnostičkim procedurama i konsultacijama, što ukazuje na odloženo donošenje kliničkih odluka. Regresiona analiza je pokazala da je korištenje elektronskog zdravstvenog kartona značajan prediktor kraćeg boravka na hitnom odjeljenju, dok su dijagnostičke procedure i prijemi na odjele intenzivne njege bili povezani s produženim boravkom. Zaključak: nalazi ove studije pokazuju da su međubolnički transferi koji su uključivali upotrebu elektronskog zdravstvenog kartona bili povezani sa značajno kraćim boravkom na hitnom odjeljenju u poređenju s transferima bez upotrebe elektronskog zdravstvenog kartona. Dobiveni rezultati podržavaju implementaciju elektronskog zdravstvenog kartona kao strategije za optimizaciju pravovremenosti i efikasnosti rada hitnog odjeljenja tokom međubolničkih transfera pacijenata.

Ključne riječi: elektronski zdravstveni karton, pravovremenost njege, međubolnički transferi

INTRODUCTION

Electronic health records are digital collections of a patient's health information that significantly enhance the quality of healthcare (1). Their interoperability, which enables seamless data exchange among diverse healthcare providers, improving care coordination and leading to better health outcomes (1,2). Furthermore, EHRs support improved clinical decision-making by providing comprehensive, real-time patient information, while also increasing patient safety through mechanisms such as reducing medication errors and preventing adverse events (3,4). Missing EHRs during interhospital transfers can result in significant issues in patient care (5).

In interhospital transfers, aside from EHRs, emergency departments also play an important role. Critically ill patients are often referred from secondary healthcare facilities to the emergency department of tertiary care centers. Such unplanned interhospital transfers are associated with an increased ED length of stay and may contribute to additional adverse clinical outcomes.When a patient is transferred to a tertiary care center, the emergency department evaluates the patient's condition and decides the necessary level of care, whether inpatient, intensive care unit, or other specialized services (6).The emergency department also coordinates with other hospital departments to ensure a seamless transition of care (7). Emergency department timeliness of care serves as the key indicator of the department's operational efficiency. It is commonly evaluated using the ED LOS, defined as the time interval between a patient's arrival and their departure from emergency department (8).

The implementation of electronic health records in hospitals has prompted considerable interest among clinicians and researchers regarding their potential to enhance patient care (9), but there is a significant gap in research concerning the impact of electronic health records on emergency department timeliness of care, particularly in the context of interhospital transfers.

AIM

The aim of this study was to evaluate the importance of electronic health records for emergency department timeliness of care in interhospital transfers of adult patients.

MATERIALS AND METHODS

Data on 137 interhospital transfers of patients aged ≥18 years, who were admitted from six hospitals at the secondary level of healthcare to the emergency department of a tertiary clinical center between 1 December 2024 and 28 February 2025, were retrospectively analyzed. Patients were divided into two cohorts based on the use of electronic health records: IHT with EHR and IHT without EHR.Various clinical and demographic data were recorded.

Continuous variables were compared using the independent sample t-test in the case of a normal distribution of data or the Mann-Whitney U test in the case of a non-normal distribution of data and are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), respectively.The Chi-square test was used to compare categorical variables, which are presented as percentages. Specifically, the t-test was applied to compare age between groups, while the Mann-Whitney U test was used for emergency department length of stay.The Chi-square test was used for categorical variables, including gender, type of case (surgical vs. non-surgical), diagnostics, consultations, ICU admissions, and ward admissions.

For statistical analysis, binary logistic regression was used to assess the impact of EHR on emergency department length of stay, as EHR was treated as a binary independent variable (present or absent) and ED LOS was dichotomized into patients with an ED stay of less than 1 hour and those with an ED stay of more than 1 hour.

The EHR variable was not included in the multiple linear regression model as its inclusion led to changes in the significance of key clinical variables.This phenomenon suggests potential mediation and collinearity, and therefore, EHR was analyzed separately using binary logistic regression. Multiple linear regression was applied to evaluate the influence of other variables, including age, gender, case type (surgical vs. non-surgical), diagnostics, consultations, ICU admission, and ward admission. The use of multiple regression allowed for the adjustment of potential confounders, ensuring a more accurate estimation of the independent effects of these factors on ED LOS.

RESULTS

Data on 137 patients transferred from six hospitals at the secondary level of healthcare to the emergency department of a tertiary clinical center were analyzed, with 74 patients in the IHTs with EHRs group (54.01%) and 63 patients in the IHTs without EHRs group (45.99%).

Table 1 **Comparisons of variables between two study groups**

Variables	IHT (with EHR) N=74(54.01%)	IHT (without EHR) N=63(45.99%)	p
Female n (%)	32 (23.36)	18 (13.14)	0.075
Age	66.72±18.81	58.78±15.86	0.205
Surgical cases	25 (18.25%)	24 (17.52%)	0.875
Non-surgical cases	49 (35.77%)	39 (28.47%)	0.178
Diagnostics	16 (11.68%)	32 (23.36%)	<0.001
Consultations	18 (13.14%)	30 (21.90%)	0.004
ICU admissions	12 (8.82%)	19 (13.97%)	0.182
Ward admissions	46 (33.82%)	40 (29.41%)	0.434
ED LOSminutes, median (interquartile range)	11.5 - (21.75)	37 - (61)	0.001

Data are presented as absolute numbers, mean ± standard deviations (SD) or as median (interquartile range); IHT (with EHR)-interhospital transfers (with electronic health records); IHT (without EHR)-interhospital transfers (without electronic health records); ICU-intensive care unit; ED LOS-emergency department length of stay

Comparisons of variables between two study groups showed that IHTs with EHRs was associated with a significantly shorter ED LOS compared to IHTs without EHRs (Median 11.5, IQR 21.75 vs. Median 37, IQR 61; $p < 0.001$). Patients without EHR underwent more frequent diagnostic procedures (23.36% vs. 11.68%, $p < 0.001$) and consultations (21.90% vs. 13.14%, $p = 0.004$), indicating a potentially prolonged decision-making process. Other factors, including gender, age, case type (surgical vs. non-surgical), and intensive care unit or ward admissions, showed no significant differences between groups ($p > 0.05$).

Table 2 **Binary logistic regression analysis of EHR impact on ED LOS**

Variables	B	SE	Wald	df	Sig.	Exp (B)
EHR (yes)	0.90	0.40	5.20	1	0.023	2.46
Constant	0.55	0.26	4.47	1	0.034	1.74

EHR-eletronic health record

Binary logistic regression analysis showed that the presence of EHR was a significant predictor of shorter ED LOS. The regression coefficient for EHR was B = 0.90 (SE = 0.40), with a Wald statistic of 5.20 (df = 1, p = 0.023). The odds ratio was EXP (B) = 2.46, indicating that patients with EHR had 2.5-fold higher odds of a shorter ED LOS compared to those without EHR.

Multiple linear regression analysis revealed that diagnostics (B = 59.47, p = 0.008) and ICU admissions (B = 62.32, p = 0.016) were significant predictors of prolonged ED LOS. Consultations (B = 40.68, p = 0.085) showed a marginal association. Other variables, including gender, age, case type, and ward admissions, were not significantly associated with ED LOS (p > 0.05).

Table 3 **Multiple linear regression analysis of predictors of ED LOS.**

Model	Unstandardized coefficient		Std. coeff.	t	p
	B	Beta	Std. error		
Gender (f)	7.32	0.03	17.52	0.42	0.677
Age (years)	-0.24	-0.04	0.47	-0.51	0.613
Surgical cases (n)	-39.63	-0.18	100.42	-0.39	0.694
Non-surgical cases (n)	-18.34	-0.08	101.70	-0.18	0.857
Diagnostics (yes)	59.47	0.26	22.20	2.68	0.008
Consultations (yes)	40.68	0.18	23.42	1.74	0.085
ICU admissions (yes)	62.32	0.24	25.62	2.43	0.016
Ward admissions (yes)	0.81	0	22.52	0.04	0.971
Constant	38.17		106.98	0.36	0.722

ICU-intensive care unit

DISCUSSION

This study investigated the impact of electronic health records on emergency department timeliness of care in interhospital transfers of adult patients, who were admitted from six hospitals at the secondary level of healthcare to the emergency department of a tertiary clinical center between 1 December 2024 and 28 February 2025. We found that interhospital transfers with EHRs were associated with a significantly shorter emergency department length of stay compared to IHTs without EHRs. Patients without EHR underwent more frequent diagnostic procedures and consultations, indicating a potentially prolonged decision-making process. Binary logistic regression analysis showed that the presence of EHR was a significant predictor of shorter ED LOS. The importance of these findings is that the implementation of EHRs in IHTs reduces emergency department length of stay and improves operational efficiency during the transfer process.

The EHR variable was not included in the multiple linear regression model because its inclusion led to changes in the significance of key clinical variables. This phenomenon suggests potential mediation and collinearity, and therefore it was necessary to assess the impact of EHR on emergency department length of stay separately using binary logistic regression analysis. Multiple linear regression was applied to evaluate the influence of other variables, including age, gender, case type (surgical vs. non-surgical), diagnostics, consultations, ICU admission, and ward admission. The use of multiple regression allowed for the adjustment of potential confounders, ensuring a more accurate estimation of the independent effects of these factors on ED LOS.

The implementation of electronic health records in hospitals has prompted considerable interest among clinicians and researchers regarding their potential to enhance patient care (9). Specifically, EHRs are perceived as valuable tools for enabling real-time access to patient data and facilitating more efficient information sharing across healthcare settings. Despite these anticipated benefits, the empirical evidence on the influence of EHR use on the quality of patient care remains inconclusive (10,11). Several studies have linked EHR adoption to positive outcomes, including enhanced documentation practices, streamlined clinical processes (12), improved quality in ambulatory care, and greater efficiency in terms of cost and resource utilization (11). These findings suggest that EHRs can support more coordinated and evidence-based care delivery. However, the implementation of EHR systems has also been associated with significant challenges. Notably, increased documentation time has been reported, which may contribute to clinician burnout and reduce the time available for direct patient interaction (10, 13). A review of the relevant literature reveals a significant gap in research regarding the impact of electronic health records on emergency department timeliness of care, particularly in the context of interhospital transfers. For instance, the study by Chen KC, et al. (2023) evaluated the impact of interhospital transfers on ED timeliness; however, it did not specifically address the role of EHR systems in this process (8). Another study, Ravi A, et al. (2023), reveals that the implementation of an integrated consult order within the electronic health record significantly improved emergency department efficiency by reducing length of stay and enhancing user satisfaction. The study supports the use of targeted EHR interventions to streamline communication and coordination between emergency physicians and consulting services, ultimately optimizing patient flow in the ED (14).

Nonetheless, our study demonstrates statistically significant findings, particularly in the reduction of ED LOS among interhospital transfer patients with EHR-supported transitions. This supports the premise that timely access to clinical documentation facilitates more efficient triage and care coordination, thereby enhancing ED workflow.

Our study has several important limitations that must be acknowledged. First, variability in clinician experience in emergency departments may have independently influenced patient assessment and management times, potentially confounding the relationship between EHR use and emergency department length of stay. Furthermore, the study lacks adjustment for patient clinical severity. Patients with more severe or complex conditions may require prolonged evaluation, regardless of EHR availability. Lastly, the study does not evaluate long-term outcomes, including hospital length of stay, morbidity, mortality, and readmission rates.

CONCLUSION

The findings of this study demonstrate that interhospital transfers with electronic health record-supported transitions are associated with a significantly shorter length of stay in the emergency department compared to transfers without EHR support. Given that ED timeliness of care is a critical indicator of operational efficiency, as assessed by length of stay, the integration of EHRs appears to play an important role in enhancing the efficiency of emergency care. Furthermore, patients undergoing diagnostic procedures and those admitted to the intensive care unit experienced prolonged ED LOS, while consultations showed a potential impact but were not statistically significant. These findings support the implementation of electronic health records as a strategy to optimize emergency department timeliness and efficiency in interhospital transfers.

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The Impact of COVID-19 on Inflammatory Indicators and Hematological Indices in Women with Breast Cancer

Utjecaj COVID-19 na inflamatorne pokazatelje i hematološke indekse kod žena s rakom dojke

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ABSTRACT

Introduction: COVID-19 infection is a viral respiratory infection that can lead to a series of organic damages, primarily the lungs, and cause a series of complications depending on the presence of comorbidities. Given the weakened immunity in oncology patients, previous studies have reported a worse prognosis for patients with malignant tumors, such as breast tumors. Aim: to assess the usefulness of variety of inflammatory markers and hematological indices in monitoring of health status of breast cancer patients with COVID-19. Material and methods: the cross-sectional, observational analysis of the breast cancer patients diagnosed with COVID-19 in Sarajevo, Bosnia and Herzegovina, was performed in the period from 1 July 2020 to 1 November 2024. Results: values of neutrophils, lymphocytes and CRP were significant ($p < 0.05$) compared to platelets, AST, ALT and De Ritis which were not significant in all four groups of patients defined by NLR values. Values of monocytes were significant by mean value ($p < 0.05$) but not significant by median in all four groups of patients defined by NLR values ($p > 0.05$). Our findings indicate that NLR exhibits a positive correlation with MLR, SII, SIRI and AISI. Conclusion: all of these hemogram derived indices and inflammatory markers are easily accessible and cheap, which allows for their simple implementation to facilitate medical decision-making for doctors in centers with limited access to specific analyses and tertiary diagnostics.

Keywords: COVID-19, coronavirus, breast cancer, hematological indices, inflammatory markers

SAŽETAK

Uvod: COVID-19 infekcija je virusna respiratorna infekcija koja može dovesti do niza organskih oštećenja, primarno pluća, te izazvati niz kompikacija ovisno i od prisustva komorbiditeta. S obzirom na oslabljen imunitet kod onkoloških pacijenata, prethodne studije su izvjestile lošiju prognozu pacijenata sa malignim tumorom, kakvi su tumori dojke. Cilj: procijeniti korisnost različitih inflamatornih markera i hematoloških indeksa u praćenju zdravstvenog stanja pacijenata oboljelih od raka i COVID-19. Materijali i metode: provedena je presječna, opservacijska analiza pacijenata oboljelih od karcinoma dojke s dijagnosticiranim COVID-19 sa područja Sarajeva, Bosna i Hercegovina, u periodu od 1. jula 2020. do 1. novembra 2024. godine. Rezultati: vrijednosti neutrofila, limfocita i CRP-a bile su značajne ($p < 0.05$) u poređenju sa trombocitima, AST, ALT i De Ritis omjerom, koji nisu bili značajni u sve četiri grupe pacijenata definiranih prema NLR vrijednostima. Vrijednosti monocita bile su značajne po srednjoj vrijednosti ($p < 0.05$), ali nisu bile značajne po medijani u sve četiri grupe pacijenata definiranih prema NLR vrijednostima. Naši rezultati ukazuju na to da NLR pokazuje pozitivnu korelaciju sa nekoliko indeksa, uključujući MLR, SII, SIRI i AISI. Zaključak: svi ovi indeksi izvedeni iz hemograma i inflamatorni markeri su lako dostupni i jeftini, što omogućava njihovu jednostavnu primjenu kako bi se olakšalo donošenje medicinskih odluka doktorima u centrima s ograničenim pristupom specifičnim analizama i tercijarnoj dijagnostici.

Ključne riječi: COVID-19, koronavirus, karcinom dojke, hematološki indexi, inflamatorni pokazatelji

INTRODUCTION

COVID-19, caused by the coronavirus SARS-CoV-2, emerged in late 2019 and rapidly evolved into a global pandemic that profoundly impacted public health, economies, and daily life across the globe. Initially identified in Wuhan, China, COVID-19 spread quickly, leading to widespread illness and significant mortality (1). The clinical spectrum of COVID-19 varies widely, ranging from asymptomatic cases to severe respiratory illness requiring hospitalization. Common symptoms include fever, cough, fatigue, and loss of taste or smell, while severe cases may lead to pneumonia, acute respiratory distress syndrome (ARDS), and systemic illness with multi-organ failure (2). In response to the pandemic, governments around the world implemented various measures, including lockdowns, travel restrictions, and social distancing guidelines, aimed at mitigating the spread of the virus (3).

The mechanisms through which COVID-19 can cause severe complications include not only direct infection of the respiratory system but also systemic effects that involve an increase in inflammatory parameters and disruptions in hematological indices. Certain inflammatory markers and hematological parameters, including the number of leukocytes, platelets, erythrocyte, hemoglobin, play a key role in assessing the immune response and overall condition of patients. Monitoring changes in NLR (ratio between absolute number of neutrophils and lymphocytes), PLR (ratio between number of platelets and lymphocytes), LCR (ratio of number of lymphocytes and CRP value), CLR (ratio of CRP value and number of lymphocytes), SII (neutrophils×platelets/lymphocytes), SIRI (neutrophils×monocytes/lymphocytes), AISI (neutrophils×plateletsxmonocytes/lymphocytes), MLR (ratio between monocytes and lymphocytes), MNR (ratio between monocytes and neutrophils), and LMR (ratio between lymphocytes and monocytes) over the course of the disease provide valuable information regarding disease progression or resolution, allowing for adjustments to treatment plans (4).

Raised neutrophile count is correlated with severity of disease which means that NLR can be useful early prognostic marker. NLR showed its prognostic value in cardiovascular disease, infections, inflammations and some types of cancer. Because of that we took the values of NLR to be the foundation of the division of our participants based on the severity of the COVID-19 by the fact that the physiological mean value of NLR is from 1.85 to 2.15 (range from 1.00 to 2.30 which can be age and race dependent). Values below 0.7 and above 2.5 are classified as pathological and those below 0.1 are reflecting critical status. Guidelines, already used in Croatia were followed, which represent the classification of COVID-19 disease into 5 groups, similar to others, but the MEWS score is used as the basis for the classification (5-8).

While the COVID-19 pandemic had a significant impact on the healthcare system and the treatment of all diseases, we must not forget that we continue to face serious oncological conditions, such as breast cancer, which require our full attention and adequate medical support. In individuals, with breast cancer, who already have changes of parameters in their blood values due to treatment of primary disease, may experience changes in these values, which could show that their condition is getting worse or that they have a higher risk of complications from a COVID-19 infection (9).

AIM

The aim of the research was to assess the usefulness of variety of inflammatory markers and hematological indices in monitoring of health status of patients with breast cancer with COVID-19.

MATERIALS AND METHODS

This retrospective, cross-sectional, observational analysis of the breast cancer patients diagnosed with COVID-19 in Sarajevo, Bosnia and Herzegovina, was performed in the period from 1 July 2020 to 1 November 2024. We gathered patients' data based on medical documentation (complete medical history records) in primary healthcare units of the Sarajevo Canton Health Centre. The general and demographic data of patients including age, education level, marital status were collected. Laboratory results of hematological and biochemical analyzes were also collected. Hemogram and inflammatory indices (NLR, PLR, LCR, CLR, SII, SIRI, AISI, MLR, MNR and LMR) were calculated.

The cohort included a total of 166 women, but after applying the exclusion criteria, 66 were excluded from the research. The obtained data were compared between the four groups of breast cancer patients with COVID-19. Based on the study conduted by Zahorec R, et al., the the subjects were divided into four groups based on NLR value (6). The first group consisted of asymptomatic COVID-19 and very mild COVID-19, with a mean value of 1.92 (range 1.8 - 2.0); and a mean value of 2.08 (range 1.83 - 2.32). The values of NLR in the asymptomatic group could be in physiological range from 1.0 to 2.4 or slight increase of value from 2.4 to 3.0. The second group represented moderate COVID-19, with a mean value of 3.06 (range 2.33 - 3.78). The third group was moderately severe COVID-19, with a mean value of 4.79 (range 3.79 - 5.80). The fourth group involved severe and critically severe COVID-19, with a mean value of 6.79 (range 5.81 - 7.78); and a mean value of 9.90 (range 7.79 - 12.0).

Inclusion criteria were women from Sarajevo diagnosed with breast cancer, with completed chemotherapy at least 3 months before the start of the research and women with full medical history record data. Exclusion criteria were men diagnosed with breast cancer and women with incomplete medical history record data.

This study was conducted in accordance with the guidelines of the Helsinki Declaration and it was approved by the Ethics Committee of the Clinical Center University of Sarajevo (06-04-9-19265) and the Sarajevo Canton Health Center (01-03-3734-5/21 and 01-06-33-2-48-2/24).

Statistical analysis was conducted using IBM SPSS Statistics v. 17.0. To ensure the validity of our statistical methods, the study used the Kolmogorov-Smirnov test and the Shapiro-Wilk test to evaluate the normality of the distribution of the variables. Descriptive statistics were calculated to summarize and present the central tendency and variability of selected parameters. These included: Neutrophils, Lymphocytes, Monocytes, Platelets, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT). The ANOVA test was used to compare the mean values of the parameters among the 4 investigated groups of patients. Correlation was performed using the Spearman test. A p-value<0.05 was established as the threshold for statistical significance.

RESULTS

According to our total sample (n = 100), mean of women's age was 57.78 with standard deviation of 18.99. Median for age was 61.00 compared to mode which was 36.00. Range of age was 70 with the minimum of 20 and maximum of 90.

Neutrophils value had mean value of 60.88 ± 10.55, as shown in Table 1. Lymphocytes had mean value of 28.76 ± 8.82. Monocytes had mean value of 6.87 ± 2.89. Platelets had mean value of 267.22 ± 95.18.

CRP had mean value of 2.47 ± 5.36. AST had mean value of 27.66 ± 35.21. ALT had mean value of 27.86 ± 33.95. De Ritis ratio had mean value of 1.08 ± 0.43.

Mean value for NLR was 2.65 ± 1.91. Median for NLR value was 2.65 compared to mode which was 1.18. Range for NLR value was 9.76 with minimum value of 0.96 and maximum value of 10.72.

Table 1 **Descriptive statistics of selected parameters for breast cancer patients with COVID-19.**

Descriptive Statistics

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Neutrophiles	100	52.20	35.70	87.90	60.88	10.55
Lymphocytes	100	37.80	8.20	46.00	28.76	8.82
Monocytes	100	12.00	1.60	13.60	6.87	2.89
Platelets	100	703.00	105.00	808.00	267.22	95.18
CRP	100	27.00	.01	27.13	2.47	5.36
AST	100	241.00	12.00	253.00	27.66	35.21
ALT	100	233.00	8.00	241.00	27.86	33.95
De Ritis ratio	100	3.25	.40	3.65	1.08	.43
Valid N (listwise)	100					

Most of the patients from asymptomatic and very mild COVID-19 group were from 65+ with 23 patients from this age group, followed by 22 patients from 41-65 age group.

Most of the patients from moderate COVID-19 group were from 65+ group (with 12 patients), followed by patients from <30 years age group (8 patients).

Most of the patients from moderately severe COVID-19 group were from 41-65 age group (4 patients), followed by 2 patients from 65+ age group.

Most of the patients from severe and critically severe COVID-19 group were 65+ (with 4 patients), followed by 2 patients from 41-65 age group.

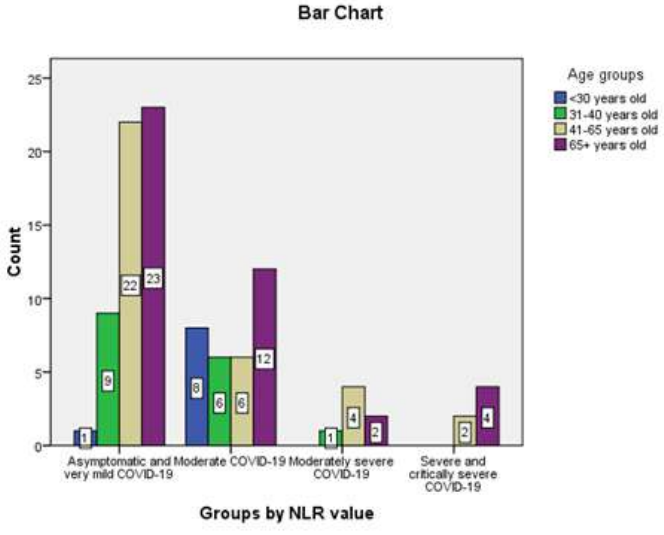

Figure 1 **Age groups according to severity of disease.**

Median (IQR) values of neutrophils were statistically significant in all four groups of patients defined by NLR values ($p < 0.05$). Patients who were in the severe and critically severe COVID-19 group had the mean neutrophils value of 77.12 ± 13.50. Range for Neutrophils was 33.50 with minimum of 54.40 and maximum of 87.90.

Median (IQR) values of lymphocytes were statistically significant in all four groups of patients defined by NLR values ($p < 0.05$). Patients who were from asymptomatic and very mild COVID-19 group had the mean lymphocytes value of 35.04 ± 5.14. Range for lymphocytes in this group was 24.10 with minimum of 21.10 and maximum value of 46.00.

Median (IQR) values of monocytes were statistically significant by mean value ($p < 0.05$) but not statistically significant by median in all four groups of patients defined by NLR values ($p > 0.05$). Patients who were from moderately severe COVID-19 group had mean monocytes value of 8.80 ± 1.75. Range for monocytes in this group was 4.60 with minimum of 6.40 and maximum of 11.00.

Median (IQR) values of platelets were not statistically significant in all four groups of patients defined by NLR values ($p > 0.05$). Patients who were from moderate COVID-19 group had mean value for platelets of 275.46 ± 86.19. Range for platelets in this group was 409.00 with minimum of 157.00 and maximum value of 566.00.

Median (IQR) values of CRP were statistically significant in all four groups of patients defined by NLR values ($p < 0.05$). Patients from severe and critically severe COVID-19 group had mean CRP value of 6.22 ± 10.92. Range for CRP in this group was 27 with minimum of 0 and maximum of 27.

Median (IQR) values of AST were not statistically significant in all four groups of patients defined by NLR values ($p > 0.05$). Patients from severe and critically severe COVID-19 group had mean AST value of 38.00 ± 33.96. Range for AST in this group was 89.00 with 18.00 as minimum and 107.00 as maximum value.

Median (IQR) values of ALT were not statistically significant in all four groups of patients defined by NLR values ($p > 0.05$). Patients who were in severe and critically severe COVID-19 group had mean ALT value of 38.66 ± 32.99. Range for ALT in this group was 85.00 with minimum of 18.00 and maximum value of 103.00.

Median (IQR) values of De Ritis ratio were not statistically significant in all four groups of patients defined by NLR values ($p > 0.05$). Patients who were from severe and critically severe COVID-19 had mean value for De Ritis ratio of 1.06 ± 0.34. Range for De Ritis ratio in this group was 0.99 with minimum of 0.40 and maximum of 1.39.

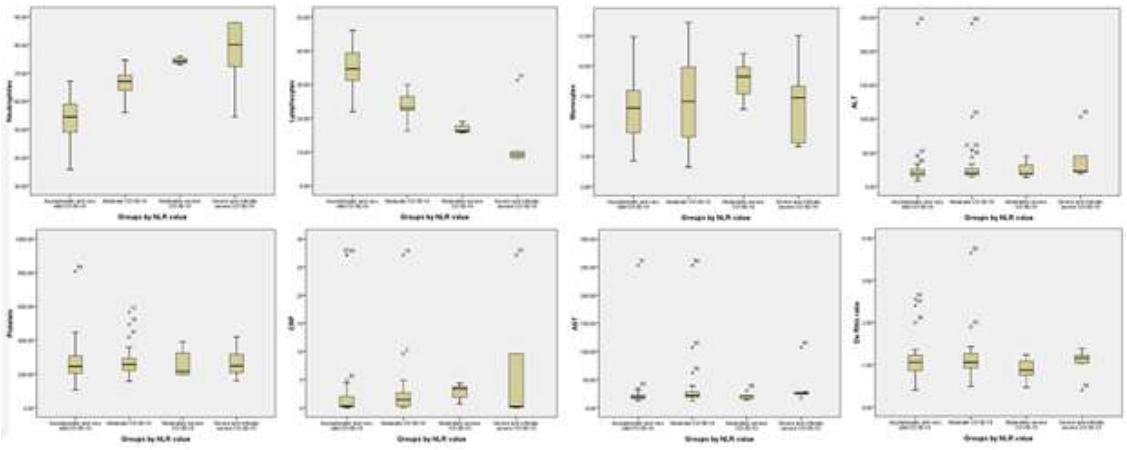

Figure 2 **Boxplots of examined laboratory parameters in patient groups.**

NLR did not have statistically significant correlation with PLR, LCR and CLR. PLR had positive correlation with LCR but not with NLR and CLR. LCR had statistically significant correlation with PLR but not with NLR and CLR. CLR did not have correlation with NLR, PLR and LCR.

DISCUSSION

The intersection of COVID-19 and breast cancer presents a uniquely vulnerable patient population, where immunosuppression from malignancy and treatment regimens may exacerbate the impact of viral infection. In this study, we evaluated laboratory parameters and clinical data to better understand the association between COVID-19 severity and hematologic, inflammatory, and hepatic markers in breast cancer patients. The average age of patients in our study was 57.78 years, with a wide range from 20 to 90 years, indicating that both younger and older breast cancer patients are susceptible to COVID-19. A significant proportion of patients with asymptomatic or very mild COVID-19 were over 65 years old, a finding that aligns with literature indicating increased COVID-19 risk with age and comorbidities (10).

Analysis of laboratory parameters revealed significant differences across COVID-19 severity groups. Neutrophil levels were elevated in patients with severe and critically severe disease, with a mean of 77.12 ± 13.50, while lymphocyte counts were notably reduced. These findings are consistent with previous studies demonstrating that elevated neutrophils and reduced lymphocytes are indicative of heightened systemic inflammation and immune dysregulation, both hallmarks of severe SARS-CoV-2 infection (11).

The neutrophil-to-lymphocyte ratio (NLR), which reflects the balance between pro-inflammatory and regulatory immune responses, showed statistically significant differences across disease severity groups. The mean NLR in our total sample was 2.65 ± 1.91, with higher values seen in more severe COVID-19 cases. NLR has been widely recognized as a prognostic biomarker for adverse outcomes in COVID-19, especially among patients with underlying malignancies such as breast cancer (12).

Similarly, C-reactive protein (CRP), another key inflammatory marker, was significantly elevated in patients with more severe forms of COVID-19, particularly those in the severe and critically severe group, with a mean of 6.22 ± 10.92. CRP is an acute-phase reactant that correlates with systemic inflammation and tissue injury. This aligns with other studies showing that high CRP levels are associated with poor COVID-19 outcomes (13).

On the other hand, liver enzymes such as AST and ALT, as well as the De Ritis ratio (AST/ALT), did not show statistically significant differences between COVID-19 severity groups. The lack of significant hepatic enzyme elevation suggests limited liver involvement in this breast cancer cohort, although isolated case reports have noted hepatotoxic effects in COVID-19 patients. The mean AST and ALT values in the most severely affected group were 38.00 ± 33.96 and 38.66 ± 32.99, respectively, which do not strongly suggest hepatic failure or major liver damage in the context of COVID-19 (14).

Monocyte levels were statistically significant by mean value but not by median in patients grouped by NLR, particularly elevated in moderately severe COVID-19 cases. Monocytes, while less frequently analyzed than neutrophils or lymphocytes, play an important role in viral antigen presentation and cytokine production. Their role in COVID-19 pathogenesis, particularly among cancer patients, is still under active investigation (15).

Interestingly, platelet levels and associated ratios such as PLR (platelet-to-lymphocyte ratio) did not show consistent trends across severity groups. While some literature supports the role of thrombocytopenia and elevated PLR as prognostic indicators in COVID-19, our findings suggest these markers may be less reliable in breast cancer patients, who often exhibit altered platelet dynamics due to malignancy and treatment (10).

Furthermore, correlation analysis showed that NLR had no significant relationship with PLR, LCR (lymphocyte-to-CRP ratio), or CLR (CRP-to-lymphocyte ratio). PLR was only correlated with LCR, not with NLR or CLR. These findings suggest that among inflammatory biomarkers, NLR might be more specific and independently predictive of COVID-19 severity in breast cancer patients, supporting its use in clinical decision-making (12).

CONCLUSION

In summary, the study had elucidated significant differences among hematological indices and inflammatory markers, underscoring their potential utility in assessing systemic inflammation and immune response. NLR, LCR, SII, SIRI, AISI, MLR, and MNR consistently displayed positive statistical correlations, suggesting their interrelated roles in reflecting inflammatory processes. All of these hemogram derived indices and inflammatory markers are easily accessible and cheap, which allows for their simple implementation to facilitate medical decision-making for doctors in centers with limited access to specific analyses and tertiary diagnostics.

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Persistence of Human Papiloma Virus after Conization

Perzistencija Humanog papiloma virusa nakon konizacije

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ABSTRACT

Introduction: persistent high-risk human papillomavirus (HPV) infection is strongly and consistently associated with high-grade cervical intraepithelial neoplasia (CIN) and is considered crucial for the progression of cervical precancer to invasive cervical cancer (ICC). Aim: to examine the persistence of HPV infection in patients of different reproductive ages after conization. Materials and methods: the study sample consisted of a total of 100 patients, HPV genotyped and surgically treated - conization. As part of the comprehensive diagnostic workup, detection and verification of cervical dysplasia, four complementary methods play a role: PAP test, colposcopy with targeted biopsy, pathohistological analysis of the sample, HPV virus genotyping. Results: the largest number of subjects was born in the 1980s. The oldest subject was 65 years old, while the youngest was 23 years old. All subjects who were HPV negative preoperatively remained HPV negative postoperatively. The number of HPV positive subjects decreased during follow-up examinations. The most common HPV type of the virus is still HPV type 16. Conclusion: by monitoring HPV status in this study, we conclude that patients who are HPV positive with type 16 have an increased risk of residual or recurrent cervical intraepithelial neoplasia.

Keywords: human papilloma virus, cervical cancer, conization

SAŽETAK

Uvod: perzistentna visokorizična infekcija humanim papiloma virusom (HPV) snažno je i konzistentno povezana sa intraepitelnom neoplazijom grlića materice visokog stepena (CIN) i smatra se ključnom za progresiju prekancera grlića materice u invazivni rak grlića materice (ICC). Cilj: ispitati perzistentnost HPV infekcije kod pacijentica različite generativne dobi nakon konizacije. Materrijali i metode: ispitivani uzorak je sačinjavalo ukupno 100 pacijentica, HPV genotipiziranih i operativno tretiranih - konizacija. U sklopu cjelovite dijagnostičke obrade, otkrivanja i verifikacije cervikalne displazije, ulogu imaju četiri komplementarne metode: PAPA test, kolposkopija sa ciljanom biopsijom, patohistološka analiza uzorka, HPV genotipizacija virusa. Rezultati: najveći broj ispitanica je rođen 1980-ih godina. Najstarija ispitanica je imala 65. godina, dok je najmlađa imala 23. godine života. Sve ispitanice koje su preoperativno bile HPV negativne i postoperativno su ostale HPV negativne. Broj HPV pozitivnih ispitanica se smanjivao kroz kontrolne preglede. Najučestaliji HPV tip virusa je i dalje HPV tip 16. Zaključak: praćenjem HPV statusa u ovoj studiji zaključujemo da pacijentice koje su HPV pozitivne sa tipom 16 imaju povećan rizik od rezidualne ili rekurentne cervikalne intraepitelne neoplazije.

Ključne riječi: humani papiloma virus, karcinom cerviksa, konizacija

INTRODUCTION

Cervical cancer is the tenth most common cause of death among malignancies in the world, and the second most common cancer by incidence among women in Bosnia and Herzegovina, after breast cancer (1). Five-year survival for patients with early clinical stage varies from 50% to 90% according to different prognostic factors. Local recurrence of the disease is a significant cause of mortality. Recurrence is more common in women with advanced disease and in tumors with high risk factors. Recurrence usually occurs within three years of diagnosis (2).

Cervical cancer develops from its precursors, the so-called cervical intraepithelial neoplasia (CIN), and the most important risk factor is infection with high-risk human papillomavirus (HRHP). Almost all cases of cervical cancer are caused by persistent infection with HRHP types. Persistent HRHP infection is strongly and consistently associated with high-grade intraepithelial cervical neoplasia CIN 2/3 and is considered crucial for the progression of cervical precarcinoma to invasive cervical cancer (ICC). It is recommended that women with a histological diagnosis of CIN 2/3 receive ablative or excisional therapy to eliminate HPV-associated CIN. However, a proportion of CIN 2/3 cases remain infected with HRHP even after treatment. Recurrent CIN may be a consequence of inadequate treatment of precancerous lesions of the cervix, incomplete clearance of HPV infection, resulting in persistent HPV HR infection, re-infection with new HPV HR types, or persistence of another HPV type unrelated to the primary cervical lesion (3,4,5).

There is a key uncertainty in the natural history of HPV infection within an individual, whether HPV infection that is undetectable on repeat testing has truly cleared or whether the virus has persisted at low, undetectable levels or entered a latent state. While the distinction between the latter two scenarios is controversial, studies suggest that re-detection of the same HPV type is relatively common, occurring in at least 10-20% of women who are observed to have 'cleared' the virus (4,5). Furthermore, compelling data from multiple studies of immunocompromised, sexually abstinent, older, less sexually active populations, and adolescents with long-term intensive follow-up support the phenomenon of immune-controlled, re-detection or reactivation of previously acquired type-specific HPV infection (6-8). Observational data in humans are consistent with animal models of papillomavirus latency, which have quite elegantly demonstrated latent detection of low-copy papillomavirus DNA, with minimal gene expression in basal cells after clinical resolution of the initial viral infection. After iatrogenic immunosuppression, papillomavirus copy number increased in the epithelium of latently infected animals, although no recurrence of warts (result of initial infection) was observed (4,5).

To clinically monitor patients after treatment for cervical intraepithelial neoplasia, ASCCP-recommended follow-up strategi es include HPV testing, cytology, and colposcopy, alone or in combination, at three-monthly or yearly intervals. Given the higher sensitivity of HPV testing for the detection of CIN 2/3 compared to cytology or colposcopy, HPV testing is routinely used after treatme nt in many clinical practices to aid in the early detection of recurrent CIN (4).

AIM

The aim of the study was to investigate the persistence of HPV infection in patients of different reproductive ages after conization.

MATERIALS AND METHODS

The conducted research was prospective, descriptive-analytical, comparative, partly epidemiological, and mostly clinically applicable in nature. The entire research was conducted on patients treated at the Clinic of Gynecology and Obstetrics of the Clinical Center University of Sarajevo (CCUS). The research was controlled among two defined comparative groups. The studied sample consisted of a total of 100 patients, HPV genotyped and conized. The diagnosis of carcinoma was made on the basis of pathohistological examination of biopsy samples of tumor tissue from the surface of the cervix and curettage of the cervical canal. Personal history, epidemiological history, gynecological examination were recorded in all patients, and HPV genotyping was performed.

The study included all subjects treated at the Clinic of Gyneco logy and Obstetrics of the CCUS, during the three-year study period, who met the criteria for inclusion in the study. The study was based on the analysis of prospectively collected relevant data obtained from 100 HPV genotyped patients.

In the experimental part of the study, the subjects were divided into two groups of fifty subjects each, as follows:

1. Group I (n = 50): female patients of reproductive age who were HPV genotyped, conized.
2. Group II (n = 50): perimenopausal and menopausal patients who were HPV genotyped and conized.

As part of the comprehensive diagnostic and therapeutic work-up, detection and verification of cervical dysplasia, the following complementary methods played a role: pap smear, colposcopy with targeted biopsy, pathohistological analysis of the sample, preoperative HPV genotyping, conization, postoperative HPV genotyping.

HPV genotyping, which is based on PCR, was performed in two steps. In the first step, a small segment of the HPV genome was amplified in vitro. This was followed by analysis of the PCR products with various molecular methods that allow determination of the HPV genotype (9,10).

The database was compiled in Microsoft Office Excel 2013 and data from paper documentation were entered into it. After checking the integrity of the data, statistical analysis was performed in IBM SPSS Statistics v. 20.0 for Windows.

RESULTS

The study was conducted on a sample of 100 HPV-positive subjects divided into two groups of fifty subjects each. Group I (n=50), patients of reproductive age who were HPV HR positive, conized. Group II (n=50), patients in perimenopause and menopause who were HPV HR positive, conized. After the indicated and performed surgical procedure, with the aim of monitoring persistent or recurrent HPV infection, the subjects were re-genotyped for HPV 3, 6, 12 months after the surgical procedure. The largest number of respondents were born in the 1980s (n=9). The oldest respondent was 65 years old, while the youngest was 23 years old.

Table 1 **Results of preoperative HPV genotyping for all subjects.**

RESULT OF HPV GENOTYPING					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NEG	13	13.0	13.0	13.0
	POZ	87	87.0	87.0	100.0
	Total	100	100.0	100.0	

Out of 100 subjects included in this study, 13 were negative for human papillomavirus, and 87% were positive. In group I, 86% (n=43) were HPV positive, and in group II, 88% (n=44) were HPV positive.

According to their frequency in preoperative processing, the most common HPV type was 16, which was isolated alone in 30% of the subjects in group I, 44% of the subjects in group II, and in combination with other types in 30% of the subjects in group I and 12% of the subjects in group II. In the literature, the second most common high-risk HPV type 18 was present alone in 4% of the subjects in group I and in 12% of the subjects in association with other types in group I, and in group II it was present alone in 2% of the subjects and in association with 4% of the subjects. The largest number of subjects included in this research underwent a cone biopsy, 92% of them.

Table 2 **HPV genotyping results of control A – 3rd postoperative month.**

CONTROL A					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NEG	64	64.0	64.0	64.0
	POZ	36	36.0	36.0	100.0
	Total	100	100.0	100.0	

Table 2 shows the results of the HPV genotyping control A, which was performed 3 months postoperatively. Of the 100 subjects included in this study, 64 were negative for human papillomavirus, and 36% were positive. In group I, 38% (n=19) were still positive, and 62% (n=31) were negative. In group II, 34% (n=17) were still HPV positive, and 66% (n=33) were negative.

Table 3 **HPV genotyping results of control B – 6 postoperative months.**

CONTROL B					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NEG	69	69.0	69.0	69.0
	POZ	31	31.0	31.0	100.0
	Total	100	100.0	100.0	

Table 3 shows the results of the HPV genotyping control B, which was performed 6 months postoperatively. Of the 100 subjects included in this study, 69 were negative for human papillomavirus, and 31% were positive. In group I, 40% (n=20) were still positive, and 60% (n=30) were negative. In group II, 22% (n=11) were still HPV positive, and 78% (n=39) were negative. Compared to the previous control, we note that the number of newly infected is higher by one in group I, and in group II, the infection resolved in six subjects.

Table 4 **HPV genotyping results of control C - 12 postoperative months.**

CONTROL C					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NEG	73	73.0	73.0	73.0
	POZ	27	27.0	27.0	100.0
	Total	100	100.0	100.0	

Table 4 shows the results of the HPV genotyping control C which was performed 12 months postoperatively. Out of the 100 subjects included in this study, 73 were negative for human papillomavirus, and 27% were positive. In group I, 34% (n=17) were still positive, and 66% (n=33) were negative. In group II, 20% (n=10) were still HPV positive, and 80% (n=40) were negative. After 12 months compared to the previous control, we can see that there are no new infections, and that in both groups there was a withdrawal of the infection, in group I in two test subjects compared to control A, and in three test subjects compared to control B, and in group II in seven test subjects compared to control A, and in one test compared to control B. In group I, persistent infection was present in 34% of test subjects (n=17), and in group II in 20% (n=10) respondent.

Table 5 **Results of HPV genotyping of control A according to virus type by group.**

CONTROL A			Frequency	Percent	Valid Percent	Cumulative Percent
GROUP I	Valid	NEG	31	62.0	62.0	62.0
		POZ 16	6	10.0	10.0	72.0
		POZ 16,35	1	2.0	2.0	74.0
		POZ 16,45	1	2.0	2.0	76.0
		POZ 16,51,52	1	2.0	2.0	78.0
		POZ 31,33	1	2.0	2.0	80.0
		POZ 31,33,56	1	2.0	2.0	82.0
		POZ 35	1	2.0	2.0	84.0
		POZ 45	1	2.0	2.0	86.0
		POZ 51	1	2.0	2.0	88.0
		POZ 59,66	1	2.0	2.0	90.0
		POZ 66	3	6.0	6.0	94.0
		POZ 68	1	2.0	2.0	98.0
		POZ 18,39,66,68	1	2.0	2.0	100.0
		Total	50	100.0	100.0	
GROUP II	Valid	NEG	33	66.0	66.0	66.0
		POZ 16	7	14.0	14.0	80.0
		POZ 16,31,58,59	1	2.0	2.0	82.0
		POZ 31	2	4.0	4.0	86.0
		POZ 33	1	2.0	2.0	88.0
		POZ 33,52	1	2.0	2.0	90.0
		POZ 51	2	4.0	4.0	94.0
		POZ 52	2	4.0	4.0	98.0
		POZ 58	1	2.0	2.0	100.0
		Total	50	100.0	100.0	

Table 5 shows the HPV types according to frequency in the first control A, three months postoperatively by groups of subjects. The most frequent HPV type of virus is 16, which in group I was found alone in 10% (n=6) of subjects and in combination with other types in 6% (n=3) of subjects. HPV 18 was found only in group I in 2% of subjects and in association with other high-risk types.

Table 6 **Results of HPV genotyping of control B according to virus type by group.**

CONTROL B			Frequency	Percent	Valid Percent	Cumulative Percent
GROUP I	Valid	NEG	30	60.0	60.0	62.0
		POZ 16	6	12.0	12.0	74.0
		POZ 31,33	1	2.0	2.0	76.0
		POZ 31,39,68	1	2,0	2,0	78.0
		POZ 33	1	2.0	2.0	80.0
		POZ 35	1	2.0	2.0	82.0
		POZ 45	1	2.0	2.0	84.0
		POZ 51, 66	1	2.0	2.0	86.0
		POZ 52	2	4.0	4.0	88.0
		POZ 66	2	4.0	4.0	90.0
		POZ 68	2	4.0	4.0	94.0
		POZ 35,52	1	2.0	2.0	98.0
		POZ 58,66,68	1	2.0	2.0	100.0
		Total	50	100.0	100.0	
GROUP II	Valid	NEG	39	78.0	78.0	80.0
		POZ 16	4	6.0	6.0	84.0
		POZ 16,45	1	2.0	2.0	86.0
		POZ 16,52	1	2.0	2.0	88.0
		POZ 31	1	2.0	2.0	90.0
		POZ 31,33,52	1	2.0	2.0	92.0
		POZ 31,56,58	1	2.0	2.0	94.0
		POZ 33	1	2.0	2.0	98.0
		POZ 51	2	4.0	4.0	100.0
		Total	50	100.0	100.0	

Table 6 shows the HPV types according to frequency in the second control B, six months postoperatively. The most frequent HPV type of virus is still 16, which was isolated alone in 12% of the subjects in group I (n=6), and was not isolated in combination with other types. In group II, it was isolated in 6% of the subjects (n=4), and in combination with other virus types was isolated in 4% of the subjects (n=2). HPV type 18 was not isolated at all in control B, neither in group I nor in group II.

Table 7 **Results of HPV genotyping of control B according to virus type by group.**

CONTROL C			Frequency	Percent	Valid Percent	Cumulative Percent
GROUP I	Valid	NEG	33	66.0	66.0	66.0
		POZ 16	3	6.0	6.0	72.0
		POZ 16, 18	1	2.0	2.0	74.0
		POZ 31, 68	1	2.0	2.0	76.0
		POZ 31,39,68	1	2.0	2.0	78.0
		POZ 31,56	1	2.0	2.0	80.0
		POZ 33	1	2.0	2.0	82.0
		POZ 39,52,58	1	2.0	2.0	84.0
		POZ 51, 52	1	2.0	2.0	86.0
		POZ 52	2	4.0	4.0	90.0
		POZ 56	1	2.0	2.0	92.0
		POZ 66	1	2.0	2.0	94.0
		POZ 68	1	2.0	2.0	96.0
		POZ 45,58,68	1	2.0	2.0	98.0
		POZ 52	1	2.0	2.0	100.0
		Total	50	100.0	100.0	
GROUP II	Valid	NEG	40	80.0	80.0	80.0
		POZ 16	4	8.0	8.0	88.0
		POZ 16,68	1	2.0	2.0	90.0
		POZ 31	1	2.0	2.0	92.0
		POZ 31,58,59	1	2.0	2.0	94.0
		POZ 51	1	2.0	2.0	96.0
		POZ 52	1	2.0	2.0	98.0
		POZ 56	1	2.0	2.0	100.0
		Total	50	100.0	100.0	

Table 7 shows the HPV types according to frequency in the third control C, twelve months postoperatively. The most frequent HPV type of the virus is still HPV type 16, which was isolated alone in 6% (n=3) of the subjects in group I and in combination with other types in one subject. In group II, it was isolated alone in 8% (n=6) of the subjects and also in combination in one subject. Its reduced number of isolations compared to the time of sampling after surgery is noticeable. HPV type 18 was isolated in combination with HPV 16 in group I in only one subject, which indicates a new infection with this type of virus, because in control B it was not isolated in any group.

DISCUSSION

The treatment of cervical intraepithelial neoplasia grade II/III (CIN II/III), (CIN III/CIS) consists of a conservative surgical approach using the electrosurgical excision procedure (LLETZ) which guarantees surgical radicality and preserves the functional integrity of the cervix, given that young women are most affected by these pathologies. Treatment of CIN II/III or carcinoma in situ (CIS) with LLETZ is effective and most patients do not require further treatment. However, approximately 23% of patients develop CIN II/III after conservative treatment due to residual or recurrent lesions. It has been observed that women who do not eliminate HPV have a higher recurrence rate (11). In the study by Heymans et al., patients with HPV 16 were identified as being at high risk of recurrence and therefore underwent more frequent follow-up (12).

Analysis of the sociodemographic data of our respon dents revealed that the oldest respondent was 65, while the youngest was 23 years old. In group I, the largest number of respondents are between the ages of 36 and 39, and in group II, the largest number of respondents are around 42 years old. In the study by Kolben et al., the average age of patients in the LLETZ group was 31.6 years (range, 23.8 - 47.3) and 31.0 (range, 23.9 - 43.4) in the limited excision group (13), which correlates with group I in our study.

So KA, et al conducted a study to assess risk factors associated with persistent HPV HR infection in patients undergoing cervical excision for the treatment of high-grade squamous intraepithelial lesions (HSIL). A retrospective cohort study included 160 patients who underwent cervical excision for the treatment of HSIL between January and December 2014. Clinical characteristics, cervical cytology, and HPV test results were reviewed. Persistent HPV HR infections were identified within six months of treatment.

The effects of various factors such as patient age, menopausal status, parity, HPV type, and histopathological findings on persistent HPV HR infections were assessed by univariate and multivariate analyses. The average age of the patients was 38.1 ± 11.5 years (range 18–86 years). Among them, 148 (92.5%) had HPV HR infections, and persistent infections after surgical treatment were detected in 48 (32.4%) patients. Univariate logistic regression analysis showed that older age (>50 years), short duration of follow-up (<3 months), and menopause were associated with persistent HPV HR infections. Multivariate analysis showed that menopausal status was the only significant independent predictor of HPV HR persistence after treatment (p = 0.001). The authors conclude that persistent HPV HR infections were detected in approximately 30% of patients within 6 months after cervical excision for HSIL. Older patients with menopause are at increased risk of HPV HR persistence after treatment for HSIL (14).

In our study, preoperative HPV genotyping showed that in group I 86% (n = 43) were HPV positive, and in group II 88% (n = 44) HPV positive. The most common HPV type was 16, which was isolated alone in 30% of the subjects in group I, 44% of the subjects in group II, and in combination with other types in 30% of the subjects in group I and 12% of the subjects in group II. In the literature, as the second most common high-risk HPV type 18, in this study in group I it was present alone in 4% of the subjects and in 12% associated with other types in group I, and in group II it was present alone in 2% of the subjects and in 4% of the subjects in combination. In the study by Huica I, et al., HPV 16 was the most prevalent among high-risk genotypes, identified (both in single and coinfections) in 26.06% of cases, followed by HPV 18 in 17.61% and HPV 31 in 11.27% of patients (15), which correlates with the results of our study for HPV type 16, while HPV type 18 was much less prevalent in our study.

Bogani G, et al conducted a retrospective, multi-institutional study with the aim of evaluating the outcome of high-risk HPV positive and negative women affected by high-grade cervical dysplasia. Medical records of patients with high-grade cervical dysplasia, who underwent conization between 2010 and 2014, were collected. All included patients were followed for at least five years. A total of 2,966 women with high-grade cervical dysplasia were examined. The study population included 1,478 (85%) and 260 (15%) women with high-grade HPV-positive and HPV-negative cervical dysplasia, respectively. The prevalence of CIN II and CIN III among the HPV positive and negative cohorts was similar (p = 0.315).

Patients with HPV-positive high-grade cervical dysplasia had a higher risk of 5-year recurrence (after primary conization) than HPV-negative patients ($p < 0.001$), which is consistent with our study results. In multivariate analysis, HPV-negative women were at low risk of recurrence ($p = 0.018$). When comparing HPV-negative patients with HPV-positive patients, CIN III was associated with an eight-fold increased risk of recurrence ($p < 0.001$). The authors conclude that HPV-negative high-grade cervical dysplasia is not uncommon and accounts for 15% of the population in this study. These patients have a more favorable outcome than those with documented HR HPV infection. They also believe that further prospective studies are needed to confirm their data (16).

In our research, a statistically significant difference was found in the results for the degree of CIN preoperatively, i.e. for HPV negative test subjects compared to HPV positive test subjects $p < 0.001$, which means that HPV genotyping will affect the increase in the number of newly discovered cases of premalignant changes of the cervix, thus confirming the working hypothesis of the research. By analyzing the data on the therapeutic procedure in our research, we found that the largest number of subjects included in this research underwent a cone biopsy, as many as 92% of them.

Knowledge about the cancer-causing potential of HPV geno types is also increasing. The International Agency for Research on Cancer was responsible for a large epidemiological study that provided strong evidence for an association of up to 18 high-risk HPV genotypes with cervical cancer. The same agency recently listed 13 HPV genotypes in its monograph as carcinogenic group 1 series 24, but emphasized the considerable diversity among them in terms of cervical cancer risk. HPV 16 in particular seems to deserve individual consideration because of its greater propensity to persist and lead to neoplastic changes than other high-risk HPV genotypes (17), as demonstrated in our study. There is currently no clinical indication for HPV typing. Given current research trends, it is not surprising that more sophisticated screening and management algorithms based on HPV testing and typing will find their way into clinical practice in the future.

By analyzing the results of the control examinations in our study, we came to the following data. Control A, which was performed three months postoperatively, in group I 38% (n = 19) were still positive, and 62% (n = 31) were negative. In group II 34% (n = 17) were still HPV positive, and 66% (n = 33) were negative. The most common HPV type of the virus is 16, which in group I is found alone in 10% (n = 6) of the subjects and in combination with other types in 6% (n = 3) of the subjects. HPV 18 was found only in group I in 2% of the subjects, and this was associated with other high-risk types.

Control B was performed six months postoperatively and it was found that in group I 40% (n = 20) were still positive, and 60% (n = 30) were still negative. In group II 22% (n = 11) were still HPV positive, and 78% (n = 39) were still negative. Compared to the previous control, we note that the number of newly infected is higher by one in group I, and in group II the infection resolved in six subjects. The most frequent HPV virus type is still 16, which was isolated alone in 12% of subjects in group I (n = 6). It was not isolated in combination with other types. In group II it was isolated in 6% of subjects (n = 4), and in combination with other virus types it was isolated in 4% of subjects (n = 2). HPV type 18 was not isolated at all in control B Control C was performed 12 months postoperatively and it was found that in group I, 34% (n = 17) were still positive, and 66% (n = 33) were negative. In group II, 20% (n = 10) were still HPV positive, and 80% (n = 40) were negative. Twelve months after the previous check-up, we observed that there were no new infections, and that in both groups the infection had resolved, in group I in two test subjects compared to control A, and in three test subjects compared to control B, and in group II in seven test subjects compared to control A, and in one test subject compared to control B. In group I, persistent infection was present in 34% of test subjects (n = 17), and in group II in 20% (n = 10) respondent. The most common HPV type is still HPV type 16, which was isolated alone in 6% (n = 3) of the subjects in group I and in combination with other types in one subject. In group II, it was isolated alone in 8% (n = 6) of the subjects and in combination in one subject. Its reduced number of isolations compared to the time of sampling after surgery is noticeable. HPV type 18 was isolated in combination with HPV 16 in group I in only one subject, which indicates a new infection with this type of virus, because in control B it was not isolated in any group.

Our results are consistent with previous studies in that persi stent infection with HPV HR is essential for the development of precancerous lesions (18), and HPV 16 and/or HPV 18 infections are associated with the highest risk of CIN, as demonstrated in the study by Huh et al. (19). Many studies addressing this topic have shown that multiple HPV infections are associated with higher rates of cervical abnormalities, and the risk of cervical cancer is higher in patients infected with multiple HPV types than in those infected with a single HPV type. Prospective studies have shown that infection with multiple high-risk HPV types acts synergistically in cervical carcinogenesis (20). Cancers in patients infected with multiple HPV types may be more resistant to therapy than those infected with a single HPV type. A study by Mungala et al reported that the treatment failure rate of cervical cancer patients infected with multiple HPV types was five times higher than that of patients infected with a single HPV type (21). The objectives of Byun, et al.'s study were to assess risk factors for recurrence of high-grade CIN and to determine whether a specific HPV genotype predicts recurrent high-grade CIN. Between January 2010 and December 2014, 172 patients with CIN II underwent cold knife conization or loop electrosurgical excision. Recurrent lesions were histologically confirmed and considered recurrent CIN II. They compared the recurrence rate in patients with and without HPV infection after treatment. 148 (86%) patients had HPV infection before treatment. The first follow-up HPV test was performed on average 4–6 months after treatment, and the recurrence rate for high-grade CIN was 3.5%. 58 patients (33.7%) were found to have HPV infection after treatment; 14 (24.1%) of them had HPV genotype 16 and/or 18. Eleven patients had persistent HPV 16 and/or 18 infection, and 3 had new HPV 16 infection after treatment ($p = 0.001$). HPV 16 genotype was significantly associated with recurrent disease and persistent infection after treatment ($p = .013$ and $p = .054$). The authors conclude that recurrence of high-grade CIN is associated with HPV infection after treatment, and persistent HPV 16 infection is the most important factor for recurrence. Therefore, HPV vaccination for HPV 16 genotype and regular follow-up with HPV testing after treatment may be useful for preventing recurrence of high-grade CIN (22). The results of the aforementioned study are in line with the results of our study. In our study, the first HPV genotyping control was performed 3 months postoperatively. Of the 100 subjects included in this study, 64 were negative for human papillomavirus, and 36% were positive. In group I, 38% (n=19) were still positive, and 62% (n=31) were negative. In group II, 34% (n=17) were still HPV positive, and 66% (n=33) were negative. The most common HPV type was 16, which in group I was found alone in 10% (n=6) of the subjects and in combination with other types in 6% (n=3) of the subjects.

Rizzuto I, et al. conducted a study to assess predictors of persi stent cytological dysplasia and HPV HR infection at 6 months of follow-up and 3 to 5 years during routine cervical smear testing. This retrospective study included data from women treated for cervical dysplasia by large loop excision of the transformation zone (LLETZ) at Ipswich Hospital, UK, between 1 January and 31 December 2012. A total of 192 patients were included in the study. There was no association between age ($p > 0.99$), smoking ($p = 0.516$), or parity ($p = 0.382$) and abnormal cytology and/or persistent HPV HR infection at 6 months.

There was an association between positive margins ($p = 0.003$), previous LLETZ ($p < 0.001$) and dyskaryosis and/or HPV HR infection at 6 months. Only prior LLETZ treatment remained associated with abnormal cytology and persistent HPV HR infection after three to five years ($p < 0.001$). The authors conclude that clinical factors, including age, smoking, medical history, and surgical margin status, may help determine the risk of dysplasia recurrence and facilitate patient follow-up based on risk stratification (23), which correlates with the results of our study. In our study, the most frequent HPV type after six months was still 16, which was isolated alone in 12% of the subjects in group I (n=6), and was not isolated in combination with other types. In group II, it was isolated in 6% of the subjects (n=4), and in combination with other types it was isolated in 4% of the subjects (n=2). Statistical analysis of HPV genotyping samples preoperatively and control B showed that there was a statistically significant difference, positive ($p<0.001$) compared to negative. The results of the analysis did not establish a statistically significant difference between HPV positive and negative subjects in relation to postoperative PHD and control after six months. For negative or positive respondents.

As can be seen from the results of the study, persistent human papillomavirus (HPV) infection is associated with multiple HPV infections, high HPV load, HPV infection of surgical margins, and advanced age in CIN after conization. The immunological mechanism is complex and primarily relates to vaginal microecological disorders, immune escape, impaired immune response, and release of regulatory cytokines. Currently, treatment methods for postoperative persistent HPV infection include surgical treatment, antiviral treatment, vaccination, and other approaches (24).

CONCLUSION

In this study, the most common HPV type was type 16, which was isolated preoperatively alone in 30% of group I, 44% of group II. Its reduced number of isolations compared to the time of sampling after surgery is noticeable. High-risk HPV type 18, in this study, was present preoperatively in 4% of the subjects and 12% associated with other HPV types in group I, and in group II it was present alone in 2% of the subjects and in 4% of the subjects associated. We also observe a reduced number of its isolations compared to the time of sampling after surgery, as is the case with HPV type 16.

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Evaluation of the Aesthetic Outcome of Piezo Rhinoplasty

Evaluacija estetskog ishoda piezzo rinoplastike

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ABSTRACT

Introduction: rhinoplasty is one of the most common cosmetic surgical procedures in the world, performed mainly to improve the aesthetic appearance or function of the nose. Piezzo rhinoplasty represents a growing shift in the philosophy of rhinoplasty towards preserving structurally healthy anatomy and transforming existing nasal structures into aesthetic and functional ideals. The aim of the study was to evaluate the aesthetic outcome of piezzo rhinoplasty. Materials and methods: the study involved 30 patients, both sexes, of the PZU "Naša mala klinika" who underwent surgical treatment, piezzo rhinoplasty. The Rhinoplasty Outcome Evaluation served as the research instrument. Results: the average age was 34.43±10.45 years. Satisfaction with the appearance of the nose showed a significant improvement, with the mean score increasing from 1.2 before surgery (median 1.0; interquartile range 0.0–2.0) to 3.7 after surgery (median 4.0; interquartile range 3.0–4.0). The Wilcoxon signed-rank test revealed a highly significant difference ($Z = -4.688$, $p < 0.001$). Quality of life ratings markedly improved postoperatively, with the mean score rising from 0.8 before surgery (median 0.5; interquartile range 0.0–2.0) to 3.7 after surgery (median 4.0; interquartile range 3.0–4.0).The difference was highly significant ($Z = -4.830$, $p < 0.001$). Conclusion: piezzo rhinoplasty leads to significant improvements in patient satisfaction, reduced insecurity, improved quality of life, and improved facial harmony after surgery.

Keywords: Piezo rhinoplasty, patient satisfaction, quality of life, facial harmony

SAŽETAK

Uvod: rinoplastika je jedan od najčešći estetskih hirurških zahvat u svijetu, koji se izvodi uglavnom radi poboljšanja estetskog izgleda ili funkcije nosa. Piezzo rinoplastika predstavlja rastući pomak u filozofiji rinoplastike prema očuvanju strukturno zdrave anatomije i preoblikovanju postojećih nosnih struktura u estetske i funkcionalne ideale. Cilj istraživanja je bio evaluacija estetskog ishoda piezzo rinoplastike. Materijali i metode: u istraživanju je učestvovalo 30 pacijenata, oba spola PZU „Naša mala klinika" koji su podvrgnuti operativnom tretmanu, piezzo rinoplastika. Kao instrument istraživanja poslužio je Rhinoplasty Outcome Evaluation. Rezultati: prosječna starost je bila 34,43 ± 10,45 godina. Zadovoljstvo izgledom nosa pokazalo je značajno poboljšanje, sa prosječnim rezultatom koji se povećao sa 1,2 prije operacije (medijana 1,0; interkvartilni raspon 0,0–2,0) na 3,7 nakon operacije (medijana 4,0; interkvartilni raspon 3,0–4,0). Wilcoxonov test predznačenih rangova otkrio je vrlo značajnu razliku ($Z = -4,688$, $p < 0,001$). Ocjena kvalitete života značajno se poboljšala postoperativno, s prosječnim rezultatom koji je porastao s 0,8 prije operacije (medijana 0,5; interkvartilni raspon 0,0–2,0) na 3,7 nakon operacije (medijana 4,0; interkvartilni raspon 3,0–4,0). Razlika je bila vrlo značajna ($Z = -4,830$, $p < 0,001$). Zaključak: piezzo rinoplastika dovodi do značajnog poboljšanja u zadovoljstvu pacijenata, smanjenju nesigurnosti, poboljšanju kvaliteta života i poboljšanju sklada lica nakon operacije.

Ključne riječi: piezzo rinoplastika, zadovoljstvo pacijenta, kvalitet života, harmonija lica

INTRODUCTION

Rhinoplasty is one of the most common cosmetic surgical procedures in the world, performed primarily to improve the aesthetic appearance or function of the nose. According to the American Society of Plastic Surgeons, nearly 45,000 rhinoplasty procedures were performed in the United States in 2022, moving it to third place as the most popular facial plastic surgery procedure after blepharoplasty and rhytidectomy (1).

Although the purpose of rhinoplasty is to correct anatomical features that may cause discomfort, the goal is to achieve natural and harmonious aesthetic results that match the proportions of each patient, without creating striking details. Rhinoplasty can be performed using a variety of techniques, depending on the approach and goals of each patient. Conventional rhinoplasty modifies the nasal hump by opening the roof of the nasal pyramid and affecting the bone structures. The anatomy is damaged, and the structures necessary for the patient to breathe properly are disrupted. Moreover, it is not uncommon for certain imperfections, often visible and stigmatizing, to develop over time when the nose is poorly reshaped (2).

Preservation Piezo rhinoplasty represents a growing shift in rhinoplasty philosophy toward preserving structurally health anatomy and reshaping existing nasal structures to aesthetic and functional ideals (3). It is rapidly gaining popularity due to the theoretical functional and aesthetic advantages of preserving the dorsal key area and dorsal aesthetic lines.The preservation technique is more accessible with an open approach, which allows clear visualization of the deformity from the tip of the nose to the dorsum, as well as easier access to electrical instruments. The addition of a Piezo-electric device, with a series of rhinoplasty inserts, allows for more precise and accurate management of the osseocartilaginous arch, reduces the risk of surface irregularities, and thus optimizes the overall surgical outcome (4).The Piezo technique involves ultrasonic shaping of the nose. The device converts electrical current into ultrasonic oscillations that target only the bone and do not affect the soft tissue. Studies using the piezo technique have shown more precise osteotomies and increased patient satisfaction in the immediate postoperative period (5).

AIM

The aim of this study was to evaluate the aesthetic outcome of piezo rhinoplasty.

MATERIALS AND METHODS

The research is a cross-sectional study. It involved 30 patients of both sexes, who reported to "Naša mala klinika" Clinic and who underwent surgical treatment, piezo rhinoplasty.

The Rhinoplasty Outcome Evaluation (ROE) was used as the research instrument.The ROE is a simple questionnaire developed to assess satisfaction and final results of rhinoplasty. It consists of six questions, two for each factor related to the physical, emotional and social dimensions of patient satisfaction. The respondents were surveyed before the surgical treatment and six months after.

Data analysis was performed using R software (latest version, RStudio 2024.12.0+467; R Core Team, Vienna, Austria). Descriptive statistics were calculated to summarize baseline demographic and clinical characteristics, including frequencies and percentages for categorical variables, and means with standard deviations for continuous variables.The Shapiro-Wilk test was applied to assess the normality of continuous variables. For comparisons of preoperative and postoperative scores on satisfaction, insecurity, quality of life, and nasal-facial harmony, the Wilcoxon signed-rank test was used due to non-normal distributions of these ordinal data. Differences between male and female subgroups in categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate.A two-tailed p-value and p-values to indicate the significance of findings. <0.05 was considered statistically significant.

All analyses were conducted using R, and results are reported with relevant test statistics and p-values to indicate the significance of findings.

RESULTS

For the purpose of the study "Evaluation of the Aesthetic Outcome of Piezo Rhinoplasty," responses was analyzed from 30 participants, of whom 8 (26.7%) were male and 22 (73.3%) were female.The average age was 34.43±10.45 years.

Table 1 **Baseline demographic and clinical characteristics of patients by sex.**

	Total	Male	Female	p
Count	30 (100%)	8 (26.7%)	22 (73.3%)	
Age (years)	34.4±10.45	33.6±10	34.7±10.8	0.803
Chronic disease	3 (10%)	1 (12.5%)	2 (9.1%)	0.787
Allergies	3 (10%)	1 (12.5%)	2 (9.1%)	0.787

Table 1 summarizes the baseline demographic and clinical characteristics of the study population, stratified by sex.The study included a total of 30 patients, with females representing the majority (73.3%, n=22) and males accounting for 26.7% (n=8). The average age of participants was 34.4±10.45 years overall, with no significant difference between males (33.6±10 years) and females (34.7±10.8 years; p=0.803), indicating comparable age distributions across groups. Regarding comorbidities, chronic diseases were present in 10% of the total sample, affecting 12.5% of male patients and 9.1% of female patients; the difference was not statistically significant (p=0.787). Similarly, reported allergies were observed in 10% of participants overall, again with no significant sex-based difference (12.5% of males vs. 9.1% of females; p=0.787). These results demonstrate that the male and female groups were comparable in terms of age distribution and prevalence of chronic diseases and allergies at baseline.

Table 2 **Preoperative satisfaction, insecurity, quality of life, and facial harmony ratings by sex.**

		Total		Female		Male	
		N	%	N	%	N	%
How satisfied are you with the appearance of your nose	Not at all	12	40.0	10	45.5	2	25.0
	Somewhat	7	23.3	4	18.2	3	37.5
	Moderatly	6	20.0	4	18.2	2	25.0
	Very	4	13.3	4	18.2	0	0.0
	Completly	1	3.3	0	0.0	1	12.5
Do you feel insecure about the appearance of your nose	Not at all	10	33.3	9	40.9	1	12.5
	Somewhat	7	23.3	4	18.2	3	37.5
	Moderatly	6	20.0	4	18.2	2	25.0
	Very	1	3.3	0	0.0	1	12.5
	Completly	6	20.0	5	22.7	1	12.5
Rate your quality of life.	Not at all	15	50.0	13	59.1	2	25.0
	Somewhat	6	20.0	6	27.3	0	0.0
	Moderatly	8	26.7	2	9.1	6	75.0
	Very	1	3.3	1	4.5	0	0.0
	Completly	0	0.0	0	0.0	0	0.0
How would you rate the harmony of your nose with the rest of your face	Not at all	4	13.3	3	13.6	1	12.5
	Somewhat	9	30.0	7	31.8	2	25.0
	Moderatly	16	53.3	12	54.5	4	50.0
	Very	1	3.3	0	0.0	1	12.5
	Completly	0	0.0	0	0.0	0	0.0

Among the total sample, the largest proportion of participants (40.0%) reported being not at all satisfied with their nose, with this response being more common among females (45.5%) than males (25.0%). A moderate level of satisfaction (moderately) was expressed by 20.0% overall, similarly distributed between females (18.2%) and males (25.0%). A small proportion of participants reported being very satisfied (13.3%), with this response seen only among females. Only one male participant (3.3%) reported being completely satisfied. Regarding feelings of insecurity about their nose's appearance, 33.3% of patients reported feeling not at all insecure, with this response more frequent among females (40.9%) compared to males (12.5%). Conversely, 20.0% of participants felt completely insecure, slightly more frequent among females (22.7%) than males (12.5%). When rating their quality of life before surgery, half of the participants (50.0%) rated it as not at all good, a perception that was more common among females (59.1%) than males (25.0%). Notably, 75.0% of males rated their quality of life as moderately good, compared to only 9.1% of females. Few participants rated their quality of life as very good (3.3%), with none reporting it as completely good. In terms of the perceived harmony between the nose and the rest of the face, more than half (53.3%) rated it as moderate, similar among females (54.5%) and males (50.0%). A smaller percentage (30.0%) rated harmony as somewhat, while very few rated it as very (3.3%), and none rated it as completely harmonious. These findings highlight a generally low level of satisfaction and high level of insecurity regarding nasal appearance before surgery, with marked differences between female and male participants, particularly in satisfaction and perceived quality of life.

Table 3 **Postoperative satisfaction, insecurity, quality of life, and facial harmony ratings by sex.**

		Total		Female		Male	
		N	%	N	%	N	%
How satisfied are you with the appearance of your nose?	Not at all	0	0.0%	0	0.0%	0	0.0%
	Somewhat	1	3.3%	1	4.5%	0	0.0%
	Moderately	0	0.0%	0	0.0%	0	0.0%
	Very	7	23.3%	5	22.7%	2	25.0%
	Completely	22	73.3%	16	72.7%	6	75.0%
Do you feel insecure about the appearance of your nose?	Not at all	19	63.3%	14	63.6%	5	62.5%
	Somewhat	4	13.3%	3	13.6%	1	12.5%
	Moderately	2	6.7%	1	4.5%	1	12.5%
	Very	0	0.0%	0	0.0%	0	0.0%
	Completely	5	16.7%	4	18.2%	1	12.5%
Rate your quality of life after surgery	Not at all	0	0.0%	0	0.0%	0	0.0%
	Somewhat	0	0.0%	0	0.0%	0	0.0%
	Moderately	0	0.0%	0	0.0%	0	0.0%
	Very	10	33.3%	8	36.4%	2	25.0%
	Completely	20	66.7%	14	63.6%	6	75.0%
How would you rate the harmony of your nose with the rest of your face?	Not at all	0	0.0%	0	0.0%	0	0.0%
	Somewhat	0	0.0%	0	0.0%	0	0.0%
	Moderately	0	0.0%	0	0.0%	0	0.0%
	Very	10	33.3%	7	31.8%	3	37.5%
	Completely	20	66.7%	15	68.2%	5	62.5%

Regarding satisfaction with the nose appearance, a remarkable 73.3% of patients overall reported being completely satisfied postoperatively, with similar proportions in females (72.7%) and males (75.0%). An additional 23.3% rated themselves as very satisfied, and only 3.3% indicated they were somewhat satisfied; none reported being not at all or moderately satisfied after the surgery. Feelings of insecurity about the nose's appearance dramatically improved postoperatively: 63.3% overall reported feeling not at all insecure, with similar rates among females (63.6%) and males (62.5%). Only 16.7% of patients still felt completely insecure, with slightly higher rates among females (18.2%) compared to males (12.5%). Quality of life after surgery showed strong improvement, with 66.7% rating it as completely good (females 63.6%, males 75.0%), and an additional 33.3% rating it as very good. None of the patients reported not at all, somewhat, or moderately positive quality of life, indicating a uniformly positive shift. Perceptions of the harmony of the nose with the rest of the face also showed excellent postoperative outcomes: 66.7% rated it as completely harmonious (females 68.2%, males 62.5%), and 33.3% rated it as very harmonious. No patients rated facial harmony as not at all, somewhat, or moderately harmonious, highlighting a high level of aesthetic satisfaction after the procedure. These findings demonstrate significant improvements in patient satisfaction, reduced insecurity, enhanced quality of life, and improved facial harmony following surgery, with consistent positive responses across both female and male subgroups.

Table 4 **Comparison of average patient ratings before and after surgical intervention.**

	Before surgery				After surgery				Wilcoxon
	Mean	Median	Perc25	Perc75	Mean	Median	Perc25	Perc75	p
How satisfied are you with the appearance of your nose?	1.2	1.0	0.0	2.0	3.7	4.0	3.0	4.0	-4.688 <0.001
Level of insecurity about the appearance of your nose?	2.0	2.0	1.0	4.0	0.9	0.0	0.0	1.0	-2.395 0.017
Rate your quality of life.	0.8	0.5	0.0	2.0	3.7	4.0	3.0	4.0	-4.830 <0.001
How would you rate the harmony of your nose with the rest of your face?	1.5	2.0	1.0	2.0	3.7	4.0	3.0	4.0	-4.844 <0.001

Satisfaction with the appearance of the nose showed a significant improvement, with the mean score increasing from 1.2 before surgery (median 1.0; interquartile range 0.0–2.0) to 3.7 after surgery (median 4.0; interquartile range 3.0–4.0). The Wilcoxon signed-rank test revealed a highly significant difference ($Z = -4.688$, $p < 0.001$), indicating that participants were substantially more satisfied with their nose following the procedure. Feelings of insecurity about the nose's appearance significantly decreased, as reflected by the reduction in mean scores from 2.0 before surgery (median 2.0; interquartile range 1.0–4.0) to 0.9 after surgery (median 0.0; interquartile range 0.0–1.0). This change was statistically significant ($Z = -2.395$, $p = 0.017$), suggesting that surgery effectively reduced self-consciousness related to nasal aesthetics. Quality of life ratings markedly improved postoperatively, with the mean score rising from 0.8 before surgery (median 0.5; interquartile range 0.0-2.0) to 3.7 after surgery (median 4.0; interquartile range 3.0–4.0). The difference was highly significant ($Z = -4.830$, $p < 0.001$), indicating a notable positive impact of the surgery on patients' overall well-being. Finally, ratings of the harmony between the nose and the rest of the face also significantly increased, with a mean score of 1.5 before surgery (median 2.0; interquartile range 1.0-2.0) improving to 3.7 after surgery (median 4.0; interquartile range 3.0–4.0). This improvement was statistically significant ($Z = -4.844$, $p < 0.001$), suggesting enhanced facial aesthetic balance following the procedure. Overall, these findings demonstrate significant benefits of the surgery in terms of satisfaction with nasal appearance, reduced insecurity, improved quality of life, and greater harmony of facial features.

Table 5 **Postoperative patients recommendation willingness, expectation fulfillment, and concerns about scars by sex.**

		Total		Female		Male	
		N	%	N	%	N	%
Would you recommend this surgery to others?	Not at all	0	0.0%	0	0.0%	0	0.0%
	Somewhat	0	0.0%	0	0.0%	0	0.0%
	Moderately	1	3.3%	1	4.5%	0	0.0%
	Very	3	10.0%	3	13.6%	0	0.0%
	Completely	26	86.7%	18	81.8%	8	100.0%
How much has the surgery met your expectations?	Not at all	0	0.0%	0	0.0%	0	0.0%
	Somewhat	0	0.0%	0	0.0%	0	0.0%
	Moderately	0	0.0%	0	0.0%	0	0.0%
	Very	8	26.7%	7	31.8%	1	12.5%
	Completely	22	73.3%	15	68.2%	7	87.5%
Do you have any visible scars that concern you?	Not at all	0	0.0%	0	0.0%	0	0.0%
	Somewhat	1	3.3%	1	4.5%	0	0.0%
	Moderately	1	3.3%	1	4.5%	0	0.0%
	Very	3	10.0%	2	9.1%	1	12.5%
	Completely	25	83.3%	18	81.8%	7	87.5%

A large majority of participants (86.7%) reported they would completely recommend the surgery to others, with all male participants (100.0%) and most female participants (81.8%) expressing this level of endorsement. A smaller proportion (10.0% overall) indicated they would very much recommend the surgery, reported exclusively by females (13.6%). Regarding how well the surgery met expectations, 73.3% overall stated that their expectations were completely met, with this response seen in 68.2% of females and 87.5% of males. An additional 26.7% rated their expectations as very met, more common among females (31.8%) compared to males (12.5%). Concerns about visible scars were minimal: 83.3% of patients overall reported being completely unconcerned, with 81.8% of females and 87.5% of males in this category. Small proportions of participants expressed being very (10.0%), moderately (3.3%), or somewhat (3.3%) concerned, responses seen only among females or in a single male participant.

DISCUSSION

Patient satisfaction depends on gender, age, education level, culture, ethnicity and, most importantly, the patient's level of expectation. Assessment of factors that contribute to patient satisfaction is the main focus in preoperative evaluation (7). In this study, among the total sample, the largest proportion of participants before surgery, 40.0%, stated that they were not at all satisfied with their nose, with this answer being more common among women (45.5%). Only one participant stated that he was completely satisfied, and that was a man. Postoperatively, a remarkable 73.3% of patients reported that they were completely satisfied, and 23.3% rated themselves as very satisfied. Results that correlate with ours were reported by Almazov I, et al. in his study, where 96% of all respondents rated their satisfaction after rhinoplasty as excellent (8).

Evaluation of the outcome of surgery measured by patient satisfaction and quality of life is very important, especially in plastic surgery (9). When evaluating the quality of life before surgery, half of the participants (50.0%) rated it as not at all good. Quality of life after surgery showed a strong improvement, with 66.7% rating it as completely good and 33.3% rating it as very good.

Rhinoplasty has extraordinary effects on physical and mental health and also improves the functioning of the nose. In a descriptive and analytical cross-sectional study conducted by Fatemi MJ, et al., conducted from March 2009 to March 2010, data were collected from 75 subjects, aged 16 years and older, before and 6 months after rhinoplasty. According to this study, the quality of life is improved after rhinoplasty (10). In terms of feelings of insecurity about the appearance of their noses, they decreased significantly, as reflected in a decrease in average scores from 2.0 before surgery to 0.9 after surgery. This change was statistically significant. Insecurity was more pronounced in females, as expected and consistent with the literature (11). Nose-facial harmony scores also increased significantly, with an average score of 1.5 preoperatively to 3.7 postoperatively. This improvement was statistically significant and indicates improved facial aesthetic balance after the procedure.

The results of the study by Gökçe Kütük S, et al. showed favor able postoperative functional and aesthetic outcomes and improved psychosocial distress in patients undergoing rhinoplasty, regardless of the surgical technique (open vs. closed), type (primary vs. revision), and indication (cosmetic vs. functional) of rhinoplasty, which is in correlation with the results of this study (12).

CONCLUSION

The results of this study demonstrate significant improvements in patient satisfaction, reduced insecurity, improved quality of life, and improved facial harmony after surgery, with consistent positive responses in both female and male subgroups.

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Clinical and Laboratory Features of Measles During the 2024 Outbreak in the Zenica-Doboj Canton

Kliničko-laboratorijske karakteristike morbila tokom epidemije 2024. godine u Zeničko-Dobojskom Kantonu

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ABSTRACT

Introduction: measles is an acute viral disease caused by the morbillivirus, transmitted between people through respiratory droplets and person-to-person contact. When exposed to measles, the individual not only develops clinical manifestations yet is at risk for severe complications. Aim: to show clinical and laboratories features of measles during the outbreak in 2024. in Zenica-Doboj Canton. Materials and methods: this was a retrospective, descriptive study analyzing the medical records of 144 subjects diagnosed with measles who were treated at the Department of Infectious Diseases of the Cantonal Hospital Zenica from January to September 2024. Statistical analysis was performed with Microsoft Office Excel 2007 and SPSS Version software package 17. Results: during the 2024 measles outbreak, 1.300 cases of measles were reported to the Department of Infectious Diseases of CHZ. Of these, 144 patients have been hospitalized (11.07%).The majority of cases are preschool children under the age of 5 with 82 (56.94%), followed by school-aged children from 6 to 18 years with 40 subjects (27.78%), and adults over 19 years with 22 subjects (15.28%).Of these, 126 (87.50%) were unvaccinated, 14 (9.72%) with unknown vaccination status, and 4 (2.78%) vaccinated, and those only with a single dose.Conclusion: the increase in the number of measles cases was accompanied by a higher number of hospitalized patientsapproximately 10% of all reported cases in our sampleas well as an increased number of complications. In a relatively small sample, we observed one of the most severe complications of measles, accounting for 0.69%, whereas according to the CDC, such complications occur in 1 out of 1,000 measles patients globally, i.e., 0.1%. In our study, the most common complication of measles was pneumonia (17.36%), while global literature reports an incidence of approximately 5%. We report one fatal outcome among them with development of ARDS (Acute Respiratory Distress Syndrome).

Keywords: measles, laboratory parameters, complications, ADEM, vaccination

SAŽETAK

Uvod: morbilli su akutna infektivna bolest, uzrokovana morbilivirusom koji se prenosi kontaktom s osobe na osobu, kao i kapljičnim putem. Pri ekspoziciji morbilima, individue ne samo da razviju kliničku manifestaciju bolesti nego su i u riziku od razvoja komplikacija. Cilj: da se prikažu kliničke i laboratorijske karakteristike, kao i komplikacije morbila tokom epidemije u 2024.godini u Zeničko-Dobojskom Kantonu. Materijali i metode: ovo je retrospektivna, deskriptivna studija koja analizira historije bolesti 144 ispitanika sa dijagnozom morbila koji su liječeni na Odjelu za infektivne bolesti Kantonalne bolnice Zenice od januara do septembra 2024 godine. Statistička analiza je rađena u Microsoft Office Excel 2007 i SPSS sistemu verzija 17. Rezultati: tokom epidemije morbila 2024. godine u Zeničko-Dobojskom Kantonu je prijavljeno 1300 slučajeva morbilla. Od toga je hospitalizirano 144 ispitanika, što je 11.97%. Dominiraju predškolski ispitanici ispod 5 godina sa 82 (56,94%), potom školski uzrast od 6-18 godina 40 ispitanika (27,78%) i odrasli preko 19 godina- 22 ispitanika (15.28%). Nevakcinisanih ispitanika je bilo 126 (87,50%), nepoznatog vakcinalnog statusa 14 (9,72%) ,a vakcinisanih je bilo samo 4 (2,78%), i to samo jednom dozom.Zaključak: porast broja oboljelih od morbila prati i porast hospitaliziranih pacijenata, oko 10% u našem uzorku, kao i povećan broj komplikacija. Na našem relativno malom uzorku, pojavila se jedna od najozbiljnijih komplikacija morbila (ADEM), što je 0,69%, a prema CDC-u, takva komplikacija se desi u 1 na 1000 slučajeva morbila globalno, tj 0.1%. U našoj studiji, najčešća komplikacija morbila je bila pneumonija (17.36%), dok u literaturi incidenca iznosi približno 5%. Prijavljen je jedan smrtni slučaj sa razvojem ARDS-a.

Ključne riječi: morbili, laboratorijski parametri, komplikacije, ADEM, vakcinacija

INTRODUCION

Measles is an acute viral disease caused by the morbillivirus, transmitted between people through respiratory droplets and person-to-person contact. Due to its mode of transmission and its ability to remain airborne for a prolonged period, individuals become easily infected. Measles is a highly contagious respiratory illness, and its infective efficiency result in continued yearly multiple outbreaks worldwide, especially in the unvaccinated (1). When exposed to measles, the individual not only develops clinical manifestations yet is at risk for severe complications. At the global level, measles continues to be one of the leading causes of death among children under the age of 5, and survivors may experience neurological, pulmonary, and gastrointestinal complications (1,2). There is no specific antiviral therapy for the treatment of measles, medical care is supportive to help relieve symptoms (1). Measles is a helical symmetry virus, a member of the Paramyxoviridae family (3). The MEV seems to be antigenically stable, and there is no evidence that viral antigens have significantly changed much over time. This disease is found worldwide; in temperate climates, epidemics occur in late winter and early spring and affect mainly preschool children between 4 and 5 years of age. Individuals with defects in cell-mediated immunity as a result of malnutrition and poor healthcare systems, pregnant women (who are at increased risk of complications including miscarriage, premature birth, and low birth weight), as well as immunosuppressed patients with altered cellular and humoral immunity are at risk for severe, progressive MEV infection (1,4,5). The course of measles is characterized by three phases: prodromal, eruptive, and convalescent phase. The primary prodromal stage lasts 4 to 6 days and is characterized with symptoms like fever, weakness, catarrhal inflammation of the nasal mucosa, conjunctivitis, eyelid swelling, and a dry cough. Most cases might also display characteristic spots of the disease called Koplik spots, which are localized in the buccal mucosa around the second molar 2 to 3 days before the rash starts and disappear by the third day of the rash. The eruptive stage sees the appearance of a rash that may merge into larger patches over time. The rash begins behind the ears and along the hairline then spreads to the face, chest, and limbs. The convalescent stage begins 3 to 4 days after the rash starts and lasts until it fades away, by which time the fever and feeling unwell also usually subside. The disappearing rash leaves behind brown spots and may cause the skin to peel slightly. The rash may be minimal in children with measles modified by the vaccine. In typical measles, onset of symptoms is acute with high fever, headache, myalgia and abdominal pain. Some common complications due to infection with measles include pneumonia, otitis media, myocarditis, pericarditis, and encephalitis (1,3,6). Measles is most commonly diagnosed based on clinical manifestation, positive epidemiology, and laboratory findings. The diagnosis can be confirmed by a laboratory test that detects antibodies to the measles virus. Serological tests include blood tests that measure specific proteins called immunoglobulin G (IgG) and immunoglobulin M (IgM), genetic tests using reverse transcription-polymerase chain reaction techniques, and tests that can isolate the MEV itself. Detection of specific IgM antibodies in a serum specimens are evidence of acute infection and can be detected from the third day of the appearance of the rash, and remain positive for the next 30 to 60 days. IgG is detectable or reaches a titration of at least fourfold between the acute and convalescent phases. An pharyngeal or nasopharyngeal swab or urine sample is the recommended sample for RNA detection for suspected cases of measles. Detection of measles RNA in a clinical specimen can provide laboratory confirmation of infection and viral genotyping (3,7). Since there are no specific antiviral treatment of measles, the best course of action is prevention through routine immunization. Data from large meta-analyses show that measles vaccination is highly effective and safe, beeing up to 75% effective in reducing measles mortality (8). Patients with measles should be in airborne precautions until 4 days after onset of rash or for duration of illness in immunocompromised individuals (1,9).

Infection with measles during pregnancy increases the risk of miscarriage, intrauterine growth restriction, and premature birth (10,11). Maternal infection in the immediately before delivery can lead to severe congenital infectionincluding subacute sclerosing panencephalitis and death (11). There's no specific antiviral treatment for measles. However other kinds of well-researched treatments can help ease symptoms, lower the risk of complications and prevent death from measles. Supportive care includes the prevention or correction of dehydration, antipyretics and nutritional management. Breastfeeding should be continued throughout the course of the illness (1). Vitamin A deficiency is a recognized risk factor in severe measle. The World Health Organization (WHO) recommends a daily oral dose of vitamin A for two days to children with measles living in areas where vitamin A deficiency may be present. Measles can reduce serum concentrations of vitamin A, resulting in the body's inability to resist current and secondary infections associated with measles. If indicated, the first dose of vitamin A should be given at the time of initial measles diagnosis, and the next dose the following day (12). The results in Cochrane review confirm that two doses of vitamin A (200,000 IU) are associated with reductions in the risk of overall mortality and of pneumonia-specific mortality. Vitamin A has been recommended by the American Academy of Pediatrics and the World Health Organization to manage measles in hospitalized children (7,12). MEV is susceptible to ribavirin, however due to limited clinical research, routine treatment is not recommended. It may be considered for certain high-risk groups (13).

AIM

The aim of this study was to show clinical and laboratories features, so the complications of measles during the 2024 outbreak in Zenica-Doboj Canton.

MATERIALS AND METHODS

This was a retrospective, descriptive study analyzing the medical records of 144 subjects diagnosed with measles who were treated at the Department of Infectious Diseases of the Cantonal Hospital Zenica from January to September 2024. The diagnosis of measles was made based on a typical clinical presentation, a positive epidemiological history, and laboratory confirmationwith serological ELISA testing. Epidemiological data were obtained from the surveillance database of the Cantonal Hospital Zenica, Bosnia & Herzegowina. Data include demographic and socio-epidemiological characteristics, clinical characteristics, complications, laboratory parameters, C-reactive protein, white blood cell (WBC) count, differential blood count, aminotransferase and lactate dehydrogenase values, as well as the type and duration of therapy.

Statistical Analysis

Statistical analysis was performed with Microsoft Office Excel 2007 and SPSS Version software package 17. Categorical variables including age groups were represented as frequency and percentages. Mean values of continuous variables were described using arithmetic mean and standard deviation or median and percentiles depending on data distribution. Comparisons of these variables across age groups were performed using ANOVA or the Kruskal-Wallis test. The decision to accept or reject the hypothesis was made at a significance level of $\alpha = 0.05$.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Cantonal Hospital Zenica.

RESULTS

During the 2024 measles outbreak, 1.300 cases of measles were reported to the Department of Infectious Diseases of CHZ. Of these, 144 patients have been hospitalized (11.07%). The majority of cases are preschool children under the age of 5 with 82 (56.94%), followed by school-aged children from 6 to 18 years with 40 subjects (27.78%), and adults over 19 years with 22 subjects (15.28%). Of these, 126 (87.50%) were unvaccinated, 14 (9.72%) with unknown vaccination status, and 4 (2.78%) vaccinated, and those only with a single dose.

Table 1 **Comorbidities among hospitalized patients.**

Comorbidities	Number of patients (n)	Percentage(%)
Agenesis glsuprarenalis and Hypothyroidism	1	0.694
T2DM, HTA, Obesity	2	1.38
Atopic dermatitis	1	0.694
Epilepsy	2	1.38
Hydrocephalus	2	1.38
Neurologically atrisk child	3	2.08
Asthma	1	0.694
Bronchiolitis	1	0.694
Immune thrombocytopenia	1	0.694
Osteomyelitis	1	0.694
Tetralogy of Fallot, Down syndrome	1	0.694
Pulmonary valve insufficiency	1	0.694

Comorbidities of treated patients are presented numerically and as percentages.

In total, 93 (64.58%) of 144 cases were confirmed by serology. 13 subjects had negative serology (9.03%), and in 38 (26.39%) no microbiological confirmation of the disease was performed. Most of the subjects were treated symptomatically, specifically 103 (71.53%), 33 subjects (22.92%) received beta-lactam antibiotic therapy (ceftriaxone and amoxicillin/clavulanic acid), and 8 (5.56%) were treated with macrolides (azithromycin). In 121 (84.02%) patients, a chest x-ray was performed. 95 subjects (65.97%) had a normal chest X-ray, while 26 (18.06%) had pulmonary infiltrates. We report one fatal case of 18-year-old patient with cerebral palsy who suffered from fatal acute respiratory distress syndrome due to measles. Two pregnant women with measles were also treated, without the development of disease complications and no adverse events have been reported in the fetus.

Analysis of laboratory parameters

Table 2 **White blood cell, lymphocyte and plateletcount by age groups.**

Parameter	Age group (years)	N	Mean	S.D.	Min.	Max.	P value
White blood cell (WBC) ***(4.4 - 11.6 ×10 ^{9}/L)***	≤5	82	6.3	3.1	2.21	17.06	>0.05
	6–18	40	5.8	2.3	2.57	12.05	
	≥19	22	10.1	5.7	3.63	26.00	
Lymphocytes ***(30–50%)***	≤5	82	33.35	19.5	7.00	83.00	>0.05
	6–18	40	36.93	22.6	4.00	81.00	
	≥19	22	37.73	20.0	9.00	73.00	
Platelets ***(150–400 ×10 ^{9}/L)***	≤5	82	234.12	105.1	77.00	660	>0.05
	6–18	40	250.63	109.5	128	592	
	≥19	22	263.14	138.6	125	639	

N – frequency; Mean – arithmetic mean; SD – standard deviation; Min. – minimum value; Max. – maximum value; p value-statistical significance.

The white blood cell, lymphocyte and platelet count and ranges for different age groups were determined. The frequency, mean, standard deviation and ranges of these parameters, as well as p value, or statistical significance were determined (Table 2). The WBC mean values among different groups showed no statistical significance ($p > 0.05$), with pronounced variability in the ≥19 yearsaged group. Mean lymphocyte values remained within the reference interval ($p>0.05$). Also the measured platelet levels among different groups remained within the reference limits ($p>0.05$).

Table 3 **Mean values of CRP, AST, ALT, and LDH by age groups.**

Parameter	Age group(years)	N	Min.	Max.	Q1	Median	Q3	P value
CRP ***(0–5 g/L)***	≤5	82	0	100	8.75	19.50	40.50	<0.05
	6–18	40	0	91	6.25	17.00	41.00	
	≥19	22	4	75	7.75	17.00	40.25	
AST ***(17–59 U/L)***	≤5	82	15	495	45.00	55.50	77.00	<0.05
	6–18	40	12	932	45.25	57.00	79.25	
	≥19	22	32	286	40.50	53.50	64.75	
ALT ***(<50 IU/L)***	≤5	82	10	596	16.00	20.50	55.25	>0.05
	6–18	40	9	519	18.25	24.50	41.50	
	≥19	22	18	503	20.75	24.50	53.00	
LDH ***(120–246 IU/L)***	≤5	30	231	1557	350.75	475.50	510.50	<0.05
	6–18	17	189	930	427.50	545.00	616.50	
	≥19 years	11	218	642	421.00	481.00	567.00	

N – frequency; Q1 – first quartile; Median – median; Q3 – third quartile; Min. – minimum value; Max. – maximum value; p value-statistical significance.

The most common laboratory abnormalities were elevated values of C-reactive protein (CRP), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) in all age groups ($p < 0.05$). Finally, the alanine aminotransferase (ALT) levels remain within reference limits (<50 IU/L) in all age groups (Table 3).

Table 4 **Complications of measles.**

Disease complications	Number	Percentage (%)
Pneumonia	25	17.36
Bronchitis	11	7.64
Otitis media	6	4.17
Acute disseminated encephalomyelitis (ADEM)	1	0.69

Measles complications – values presented numerically and in percentages

Fourty-three cases (29.86%) of 144 developed complications; most frequently, pneumonia was reported (n =25). A central nervous system (CNS) complication of measles occurred on the seventh day of illness in an immunocompetent 9-year-old girl who had not been vaccinated. The clinical presentation was dominated by a morbilliform of a rash accompanied by fever, as well as a clear neurological deficit in the form of paraparesis. A chest X-ray was normal, and abdominal ultrasound was unremarkable. Laboratory findings showed no major abnormalities: mild leukocytosis (WBC 11.29 ×109/L) and slightly elevated CRP at 17 mg/L (reference <2.87 mg/L). A lumbar puncture was performed: the cerebrospinal fluid (CSF) was macroscopically clear and colorless, with cytological and biochemical parameters of the cerebrospinal fluidshowing 18 WBC/mm³ (reference 0-5 L/mm³), 2 erythrocytes/mm³ (reference 0 Er/mm³). Glucose levels in the CSF were 4.4 mmol/L, thus within normal limits (normal CSF glucose levels typically range from 2.6 to 4.5 mmol/L), and there was proteinorachia with protein level 1.5 g/L (reference 0.12-0.60 g/L). MRI of the neurocranium revealed demyelinating lesions.

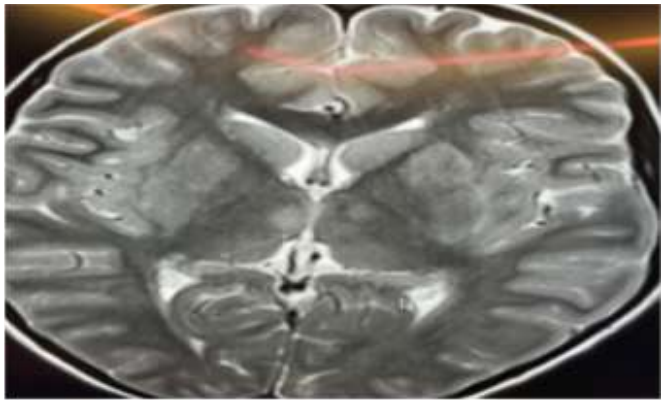

Figure **1MRI of the neurocranium - the arrow indicates demyelinating lesions (areas of altered signal intensity in the thalamus, posterior limb of the internal capsule bilaterally and asymmetrically, and in the region of the right cerebral peduncle, which according to MRI characteristics primarily correspond to demyelinating-type changes most likely consistent with ADEM).**

As the disease progressed, the clinical condition of the patient worsened. Urinary retention developed, and the neurological deficit progressed to paraplegia. The patient was transported to a tertiary level healthcare facility, the Infectious Disease Clinic of the Clinical Center University of Sarajevo. ELISA for measles showed high-titer IgM positivity. The bacteriological analysis of cerebrospinal fluid was negative. Polymerase chain reaction (PCR) for measles in CSF was not performed, as it is not available in our institution. At the tertiary center, the patient was treated with immunoglobulins and corticosteroids, with minimal regression of the neurological deficit. Later, plasmapheresis was initiated on multiple occasions, resulting in good clinical response. The patient continued with physical therapy, which led to full clinical recovery without residual neurological sequelae. Unfortunately, we do not have access to follow-up radiological evaluation of her condition.

DISCUSSION

The measles outbreak in Zenica-Doboj Canton in 2024 was accompanied by a large number of cases treated at home, while among hospitalized patients, the majority was children under the age of 5, most of whom were unvaccinated or incompletely vaccinated, or with unknown vaccination status. This aligns with World Health Organization (WHO) data from 2023, which reported approximately 107,500 deathsattributed to measles globally, mostly amongst unvaccinated or partially vaccinated children under the age of five (14). In a study from Chicago, Azan et al. during an outbreak related to migrant shelters, presented that most cases of measles were among children age <5 years, who did not have documentation of measles vaccination and were considered unvaccinated (15). A 2025 Centers for Disease Control and Prevention (CDC) report showed that most infected individuals were unvaccinated or of unknown vaccination status (16). These findings can be explained by the fact that children's immune systems are still immature, making the transmission of infectious diseases easier due to insufficient immune response to pathogens, along with frequent attendance in daycare centers which can facilitate transmission. At the same time, there is a global trend of declining childhood vaccination rates, increasing the risk of infection in this population. WHO recommends immunization for all susceptible children and adults for whom measles vaccination is not contraindicated. Coverage of 95% or greater of two doses of measles vaccine is needed in each country and community to prevent outbreaks and protect populations measles. Yet more than 22 million children missed their first dose of measles vaccine in 2023. Globally, an estimated 83% of children received their first dose of measles vaccine last year, while only 74% received the recommended second dose (14,17). Pneumonia is the most common complication of measles infection reported in literature and previous studies, caused either directly by the measles virus alone, secondary viral infection with adenovirus or HSV, or secondary bacterial infection. Results from our study follow this global trend (7). CNS complications include ADEM, measles inclusion body encephalitis (MIBE), and subacute sclerosing panencephalitis (SSPE) (18,19). ADEM is a monophasic autoimmune demyelinating disease that has an incidence of 1:1000 and occurs primarily in children over the age of 4 years (20,21). In the literature, it is more often described in adolescents and young adults after acute infection or vaccination, occurring 3-10 days after rash onset (10). The incidence of ADEM associated with measles infection is higher (1:1000) than ADEM associated with live measles vaccination (1:1,000,000) (11). Pathology is characterized by perivenular inflammation and demyelination. In the available literature, as in our case, laboratory findings are generally normal or may show mildly elevated WBC and CRP levels. CSF findings may show pleocytosis, proteinorachia, and normal glucose levels (12). CT is usually normal, while MRI is the gold standard for diagnosis, revealing lesions seen as hyperintensities on T2 and FLAIR sequences. The lesions are typically numerous and disseminated and predominantly on the white matter of the brain.

The disease course is quite unpredictable, with the possibility of complete symptom resolution within days or sometimes weeks. Mortality ranges from 10% to 25%, with the potential for lasting neurological sequelae (hearing or vision loss, paraplegia, epilepsy, or cognitive or psychological deterioration), which occur in 10–45% of patients (13). Measles-induced ADEM is a rare, life-threatening condition, and treatment decisions can be difficult as there are no clear guidelines in the literature regarding the use of corticosteroids and immunoglobulins. Most reported cases in the literature show good response to high-dose corticosteroid treatment (12). The case we presented was treated with all recommended options; however, there was no improvement in the clinical condition of the patient with high-dose corticosteroids and immunoglobulins. Clinical recovery was observed only after repeated plasmapheresis. Subacute sclerosing panencephalitis (SSPE) is a rare, non-treatable and fatal neurological complication of measles. Generally, it has been estimated that 4 to 11 in 100,000 people who get measles will eventually develop SSPE. This number goes up to 18 per 100,000 cases if the child was less than five years old when primarily infected with measles. It appears to have a higher prevalence in males, with later onset and increased latency in females. The measles vaccination will protect against SSPE as long as the person has not been exposed to the measles virus before getting the vaccine. It has been proven that to occur, there must be a direct measles infection. No cure for SSPE exists, and the condition is almost always fatal. Long-term follow-up is necessary for patients after measles infection due to the risk of developing SSPE, particularly in high-risk groups such as those with acquired immunodeficiency syndrome, babies born to those infected with measles, or those who received a full transfer of maternal measles antibodies during gestation (13). Just over half of patients had serological confirmation of the disease, as such testing was considered unnecessary due to the declared epidemic and clear clinical presentation. Likely causes of negative serology in some patients with typical symptoms in our sample include early sample collection i.e., within less than three days of rash onset. Bacterial superinfections (pneumonia, otitis media) were treated with antimicrobial therapy in accordance with pathogen type, clinical presentation, laboratory and radiological findings, which is consistent with global recommendations (17). Hematological parameters may show leukopenia, especially lymphocytopenia and thrombocytopenia, due to the viral nature of the disease (14). Our results did not show statistically significant differences in these blood parameters, possibly due to a milder clinical course, sample collection outside the acute phase, or individual immune responses. ALT medians remain within reference limits, and AST medians, although statistically significant, were very close to the upper normal limit, making the findings marginal and likely associated with the use of acetaminophen as part of symptomatic treatment, as reported in the literature (18). LDH medians significantly deviated from reference ranges ($p < 0.05$) across all age groups, with a particularly pronounced increase in children aged 6-18 years (median: 545 IU/L). Since LDH is mainly used as a marker for diverse tissue injuries and hemolysis, these results may indicate pronounced systemic inflammation or tissue damage in patients. Elevated values were not the result of extreme individual results but were consistently high in most cases, further supporting their clinical relevance. In our study, gamma-glutamyl transferase (GGT) was not analyzed due to a lack of clinical indication; however, the literature describes cases of elevated GGT values, where viral-induced cytolysis was accompanied by cholestatic liver disease and more severe clinical forms (19). Two pregnant women with measles were also treated, without developing disease complications or adverse fetal outcomes. Pregnant mothers are at higher risk of serious complications, such as pneumonia, with adverse pregnancy complications including fetal loss, premature birth, and neonatal death (10,22,23). In our study, we did not observe such outcomes, which may be attributed to high previous vaccination coverage among women of reproductive age, milder clinical presentations, infection control measures, timely treatment and hospitalization.

CONCLUSION

The increase in the number of measles cases was accompanied by a higher number of hospitalized patients - approximately 10% of all reported cases in our sample- as well as an increased number of complications. In a relatively small sample, we observed one of the most severe complications of measles (ADEM), accounting for 0.69%, whereas according to the CDC, such complications occur in 1 out of 1,000 measles patients globally, i.e., 0.1%. In our study, the most common complication of measles was pneumonia (17.36%), while global literature reports an incidence of approximately 5%. We report one fatal outcome among them with development of ARDS (Acute Respiratory Distress Syndrome). A statistically significant difference in laboratory findings was confirmed for CRP and AST levels. Serological tests were employed to assess both immunoglobulin G (IgG) and immunoglobulin M (IgM), providing an indication of immunity and potential acut infection. However, there was a longer wait for the test results, since the test was not conducted in our institution. Due to financial constraints and patients that are residents in other cantons, not all patients were tested. Due to declining vaccination rates, in future a higher number of pregnant women with measles can be expected, along with a higher risk of complications. Children whose mothers had measles during pregnancy require long-term follow-up, as they have been shown to have a higher incidence of SSPE.

LIMITATIONS

Limitations of this study include the relatively small sample size; therefore, results should be compared with studies conducted on larger samples. Only hospitalized patients were analyzed, while the actual number of infected individuals during the outbreak was significantly higher. The lack of certain data for evaluated variables due to incomplete documentation, as well as the unavailability of some diagnostic tests, limited the scope of the analysis.

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Silent Signals of the Right Heart: NT-proBNP as Prognostic Tool in Pediatric Congenital Heart Disease

Tihi signali desnog srca: NT-proBNP kao prognostički alat kod pedijatrijskih urođenih srčanih anomalija

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ABSTRACT

Introduction: early detection of postoperative complications and right ventricular (RV) dysfunction is critical in the management of pediatric patients with congenital heart disease (CHD) who have undergone primary surgical correction. This article explores the prognostic value of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in comparison to echocardiographic parameters of RV function in the follow-up of these patients. Emphasis is placed on the correlation between biochemical and imaging findings, with a focus on their respective predictive powers regarding adverse outcomes. Aim: to assess the prognostic relevance of serum NT-proBNP levels in comparison to echocardiographic parameters of right ventricular (RV) function in pediatric patients following surgical correction of congenital heart defects (CHD). Materials and methods: this single-center observational study included 100 pediatric patients who underwent surgical correction for various CHDs. NT-proBNP serum levels were measured and compared with echocardiographic indices of RV systolic function, volume overload and remodeling (e.g., TAPSE, FAC, PR index, DV/LV ratio). Correlation analyses and linear regression models were performed to determine associations. Results: NT-proBNP levels demonstrated a significant negative correlation with TAPSE ($r = -0.468$, $p < 0.001$) and FS-RVOT ($r = -0.484$, $p < 0.001$), as well as a positive correlation with mPAP ($r = 0.280$, $p = 0.032$) and DV/LV ratio ($r = 0.310$, $p = 0.002$). NT-proBNP also inversely correlated with PR index and RVOT systolic velocity. These findings indicate that NT-proBNP is a reliable marker of both RV dysfunction and volume/pressure overload in late postoperative follow-up. Conclusion: NT-proBNP offers clinically valuable, non-invasive prognostic information in pediatric CHD patients, complementing echocardiographic assessment of RV function. Its inclusion in long-term monitoring protocols may allow earlier detection of functional decline, enabling timely intervention.

Keywords: right heart, congenital heart anomaly, NTproBNP, echocardiographic analysis

SAŽETAK

Uvod: rano otkrivanje postoperativnih komplikacija i disfunkcije desne komore (DK) ključno je u liječenju pedijatrijskih pacijenata sa urođenim srčanim anomalijama (USA), koji su podvrgnuti primarnoj hirurškoj korekciji. Ovaj članak istražuje prognostičku vrijednost nivoa serumskog NT-proBNP u poređenju s ehokardiografskim parametrima funkcije DK u praćenju ovih pacijenata. Naglasak je stavljen na korelaciju između biohemijskih i slikovnih nalaza, sa fokusom na njihovu odgovarajuću prediktivnu moć u pogledu neželjenih ishoda. Cilj: procijeniti prognostičku relevantnost nivoa serumskog NT-proBNP u poređenju sa ehokardiografskim parametrima funkcije desne komore (DK) kod pedijatrijskih pacijenata nakon hirurške korekcije urođenih srčanih anomalija. Materijali metode: ova opservacijska studija u jednom centru obuhvatila je 100 pedijatrijskih pacijenata koji su podvrgnuti hirurškoj korekciji različitih USA. Serumski nivoi NT-proBNP su mjereni i upoređeni s ehokardiografskim indeksima sistolne funkcije DK, preopterećenja volumenom i remodeliranja (npr. TAPSE, FAC, PR indeks, omjer DV/LV). Korelacijske analize i modeli linearne regresije su provedeni kako bi se utvrdile asocijacije. Rezultati: nivoi NT-proBNP pokazali su značajnu negativnu korelaciju sa TAPSE ($r = -0,468$, $p < 0,001$) i FS-RVOT ($r = -0,484$, $p < 0,001$), kao i pozitivnu korelaciju sa mPAP ($r = 0,280$, $p = 0,032$) i omjerom DV/LV ($r = 0,310$, $p = 0,002$). NT-proBNP je također inverzno korelirao sa PR indeksom i sistolnom brzinom RVOT-a. Ovi nalazi ukazuju na to da je NT-proBNP pouzdan marker i disfunkcije desne komore i preopterećenja volumenom/pritiskom u kasnom postoperativnom praćenju. Zaključak: NT-proBNP nudi klinički vrijedne, neinvazivne prognostičke informacije kod pedijatrijskih pacijenata sa kongenitalnom bolešću srca, dopunjujući ehokardiografsku procjenu funkcije desne komore. Njegovo uključivanje u protokole dugoročnog praćenja može omogućiti ranije otkrivanje funkcionalnog opterećenja i disfunkcije, omogućavajući pravovremenu intervenciju.

Ključne riječi: desno srce, kongenitalna anomalija srca, NTproBNP, ehokardiografska analiza

INTRODUCION

Congenital heart defects (CHDs) are the most common conge nital anomalies in children. Surgical correction during infancy or early childhood often leads to significant improvements in clinical outcomes. However, residual hemodynamic abnormalities, particularly involving right ventricular function, may persist or develop over time. Therefore, reliable and sensitive markers are needed to monitor cardiac function and predict complications. While echocardiography remains the cornerstone of functional assessment, biomarkers such as NT-proBNP have gained attention due to their non-invasive nature and biochemical specificity (1).

NT-proBNP as a Biomarker

NT-proBNP is released from myocardial cells in response to ventricular wall stress and volume overload. Elevated levels have been associated with heart failure, pulmonary hypertension, and ventricular dysfunction. In pediatric patients, NT-proBNP levels vary with age and clinical context, but remain a promising tool for longitudinal follow-up. Their utility after surgical correction of CHD lies in their potential to signal subclinical cardiac stress before it becomes echocardiographically evident (1-3). A normal serum NTproBNP value does not mean the absence of disease, but rather indicates that the condition is compensated.

Echocardiographic Assessment of Right Ventricular Function

Echocardiography provides a direct, real-time assessment of cardiac structure and function. Key parameters for evaluating RV performance include tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and myocardial performance index (MPI). Advanced techniques such as tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) enhance sensitivity in detecting early dysfunction. Nevertheless, echocardiographic evaluation of the RV is challenging due to its complex geometry and variable load dependency (2).

Comparative Prognostic Value

Recent studies suggest that both NT-proBNP levels and echocardiographic indices are independently associated with RV dysfunction and adverse clinical outcomes. However, NT-proBNP may provide earlier warning signs in some cases, particularly when echocardiographic findings are inconclusive. Conversely, structural or regional anomalies may be better visualized with imaging. Thus, a combined approach integrating biomarker and imaging data may offer the highest prognostic accuracy (2,4).

MATERIALS AND METHODS

The research was designed as a cross-sectional, cohort, observational, prospective study, which included 100 patients aged 1-17 years, 1±17 years after primary surgical correction of congenital heart anomalies such as tetralogy of Fallot, pulmonary stenosis and atresia, transposition of the great vessels, truncus arteriosus, atrial septal defect, atrioventricular septal defect, single-chamber heart and pulmonary hypertension.

RESULTS

This study comprehensively evaluated the prognostic role of NT-proBNP in assessing right ventricular (RV) function, volume overload and chamber remodeling in pediatric patients after surgical repair of congenital heart disease. The data reflect both functional and morphological dimensions of RV status.

The respondents in the study had an average age of 8.9 ± 4.7 years (39% male). The study showed that NTproBNP was increased in 17% of patients after surgical correction of congenital heart anomalies

NT-proBNP and RV Systolic Function

The inverse correlation between NT-proBNP and TAPSE ($r = -0.468$, $p < 0.001$) reinforces the concept that reduced longitudinal RV function is associated with elevated myocardial stress. A regression model (TAPSE = 17.04 – 0.001×NT-proBNP; $R^2 = 0.259$, $p = 0.0001$) demonstrated a significant predictive relationship. This correlation was consistent with other systolic markers:

- FS-RVOT: $r = -0.484$, $p < 0.001$
- RVOT-SE: $r = -0.387$, $p = 0.002$
- S' (TDI): $r = -0.314$, $p = 0.002$

These relationships highlight NT-proBNP as a surrogate marker of RV systolic performance, particularly in long-term follow-up when structural adaptation and scarring may alter standard imaging interpretation.

Volume and Pressure Load Markers

NT-proBNP showed statistically significant positive correlations with mean pulmonary artery pressure (mPAP) ($r = 0.280$, $p = 0.032$) and inverse correlation with pulmonary regurgitation index (PR index) ($r = -0.327$, $p=0.002$), suggesting a dual sensitivity to both pressure and volume overload.
No significant correlation was observed with PHT (Pulmonary regurgitation pressure half-time) or PVR, suggesting these variables may be more dynamic or less sensitive in the chronic postoperative phase.

RV Geometry and Remodeling

NT-proBNP positively correlated with: DV/LV ratio: $r = 0.310$, $p = 0.002$ ($R^2 = 0.175$) and LEI index: $r = 0.319$, $p = 0.002$ ($R^2 = 0.053$) These morphological markers indicate RV dilation and eccentric remodeling. The observed elevation in NT-proBNP with increased RV/LV and LEI indices confirms its utility in detecting chamber remodeling, even in clinically stable patients.

Age-Related Differences

A moderate negative correlation with patient age was observed ($r = -0.294$, $p = 0.021$), indicating that NT-proBNP levels decrease over time, possibly due to myocardial adaptation or improved hemodynamics. This finding supports the role of age-adjusted interpretation when using NT-proBNP in chronic follow-up.

Descriptive Insights

The median NT-proBNP was 162 pg/mL (IQR: 81–329), with values ranging from 10 to 7217 pg/mL. This wide distribution reflects patient heterogeneity in ventricular performance and degree of residual lesions.
These findings support NT-proBNP as a robust, non-invasive biomarker that correlates with both functional impairment and morphological changes in the right ventricle post-surgical correction of congenital defects. Its strong association with echocardiographic parameters such as TAPSE, FS-RVOT, PR index, and RV/LV ratio enhances its value in clinical monitoring, especially where imaging is technically challenging.

Table 1 **Correlation between NT-proBNP and RV Remodeling Parameters.**

Parameter	Correlation (r)	p-value	Sample size (N)
TAPSE	-0.468	<0.001	100
FS-RVOT	-0.484	<0.001	96
RVOT-SE	-0.387	0.002	96
S' (TDI)	-0.314	0.002	99
PR Index	-0.327	0.002	93
mPAP	0.280	0.032	96
RV/LV ratio	0.310	0.002	93
LEI Index	0.319	0.002	96
Age	-0.294	0.021	100

	N	Minimum	Maksimum	Percentile		
				25ti	50ti (Mediana)	75ti
NTproBNP (pg/ml)	99	10.0	7217.0	81.0	162.00	329.00
TAPSE(mm)	100	9.8	28.0	15.02	16.45	18.85
FS-RVOT(%)	96	22	69	37.00	42.00	48.,00
RVOT-SE(mm)	96	0.3	1.1	0.54	0.62	0.72
IVA	98	1.04	3.40	1.72	1.97	2.49
TAI index	98	0.30	0.73	0.44	0.54	0.62
LEI index	96	1.0	2.0	1.00	1.00	1.00
E'/A' ratio	99	0.68	2.50	1.12	1.29	1.65
S' (m/sec)	99	0.06	0.15	0.09	0.11	0.12
PR index	93	0.61	0.97	0.79	0.83	0.88
DV/LV ratio	93	0.59	1.30	0,73	0.82	0.87

Table 2 **Correlations of NTproBNP with parameters that monitor right ventricular volume load in patients after surgical correction of congenital heart disease.**

Spearman's rho		mPAP	PAAT(ms)	PVR	TAPSE(mm)	FS-RVOT(%)	RV-FAC(%)	S/D	TAI index	IVA
NTproBNP	Correlation coefficient	0.210	-0.211	0.030	-0.434	-0.263	-0.270	0.095	-0.358	-0.211
	p	0.040	0.039	0.772	0.0001	0.01	0.007	0.359	0.0001	0.038
	N	96	96	97	99	96	99	96	98	97

DISCUSSION

This study assessed the prognostic relevance of NT-proBNP in predicting right ventricular (RV) function, hemodynamic burden, and anatomical remodeling in pediatric patients after repair of congenital heart defects (CHD). Our results, highlighting strong associations between elevated NT-proBNP levels and reduced RV systolic function (e.g., TAPSE r=–0.468, p<0.001) as well as markers of pressure/volume overload and dilation, align well with existing literature and extend previous findings in clinically meaningful ways.

Chowdhury RR, et al. found that NT-proBNP levels increased progressively with rising heart failure severity in children with CHD (5). Our findings are consistent in showing NT-proBNP as a sensitive marker of RV compromise, though we focused specifically on subclinical echocardiographic changes. Several studies in TOF survivors report elevated NT-proBNP in asymptomatic patients, particularly where pulmonary regurgitation or RV volume overload is present. For instance, NT-proBNP was significantly higher in children with transannular patch repair or severe regurgitation, mirroring our observation of associations with PR index.

Palm J, et al. (2021) introduced zlog-proBNP to account for age-related differences, demonstrating its strong, age-independent prognostic capacity for MACE in pediatric CHD. Although we used absolute NT-proBNP values, our study supports its prognostic utility, especially when normalized to patient age (6).

NT-proBNP has been previously correlated with exercise tolerance and RV function in post-TOF patients (7). Our study's strong negative correlation with TAPSE, FS–RVOT, RVOT SE, and tissue Doppler S velocity reinforces these observations.

The likelihood of heart failure is low when NTproBNP levels are <400 ng/L, with a negative predictive value of ~90%. However, according to the results of the study by Sagimoto M, et al., heart failure is likely when the level is >450 ng/L and the positive predictive value is also ~90% (8). Our study shows that NTproBNP is elevated in 17% of patients after surgical correction of congenital heart defects.

The increase in NTproBNP levels is independent of clinical manifestations (9). A study by Norozi K, et al. showed that NTproBNP is one of three markers (along with the Tei index during echocardiographic analysis and maximal oxygen uptake during exercise testing) of early right ventricular dysfunction, even before the onset of clinical symptoms (10).

In our study, NTproBNP levels correlated with right ventricular systolic function but not with right ventricular volume. This is consistent with the findings of Dodge- Khatami A, et al., who, using MRI, found a significant correlation between right ventricular ejection fraction and NTproBNP in children and young adults, but only a weak correlation with right ventricular volume (11).

In children with congenital heart defects, plasma BNP levels do not directly reflect the degree of ventricular pressure or volume overload, but rather reflect the degree of ventricular damage due to increased work. A normal BNP value cannot exclude any pathology, but reflects a compensated cardiac status. Our data are consistent with previous published reports and indicate that even in asymptomatic or minimally symptomatic patients, right ventricular dilatation leads to increased NTproBNP secretion, suggesting that a significant increase in NTproBNP may identify reduced cardiovascular reserve at an early stage, when patients are still clinically asymptomatic (12-15).

There is enough evidence to support the use of BNP/NT-proBNP as an adjunctive marker in the integrated evaluation of patients with congenital and acquired heart disease to help define severity and progression of heart failure as well in the monitoring of response to treatment (16,17).

RV assessment is integral to the complete evaluation, manage ment, and timing of intervention for many congenital heart lesions. The assessment of the RV can be difficult as there are no well-defined guidelines or normal values in padiatrics. RV assessments should include measuring the size of the right heart structures, quantification of RV systolic function, identification of RV diastolic function, and inclusion of TV functional analysis, with serial assessments (18,19).

Biomarkers play a crucial role in diagnosing, assessing severity, and monitoring treatment response in pediatric heart failure, similar to their adult counterparts, but with unique considerations for the pediatric population. Key biomarkers include natriuretic peptides (BNP and NT-proBNP), troponins, and newer markers like galectin-3 and GDF-15, each providing insights into different aspects of heart failure. Different types of heart failure (e.g., congenital heart disease, cardiomyopathy) may have varying biomarker profiles, requiring tailored interpretations. None of the other biomarkers reviewed were consistently superior to NT-proBNP (20-23).

Clinical Implications, Limitation and Future Directions

Our findings affirm NT-proBNP as a reliable, non-invasive biomarker for detecting RV dysfunction, even in subclinical stages. Since RV geometry assessment via echocardiography can be technically demanding, especially during long-term follow-up, NT-proBNP offers valuable adjunctive insight. Our single-center cohort with mixed CHD types limits generalizability. Age dependency remains a factor; implementing age-adjusted z-scores could enhance accuracy. Longitudinal tracking of NT-proBNP with clinical outcomes would clarify its capacity for dynamic monitoring and response to interventions. Routine postoperative monitoring of pediatric CHD patients may benefit from incorporating NT-proBNP measurement alongside echocardiographic evaluation. Establishing age- and diagnosis-specific reference values for NT-proBNP, as well as standardized echocardiographic protocols, is crucial for consistent interpretation. Further multicenter studies are needed to validate the prognostic thresholds of NT-proBNP and determine its precise role in postoperative surveillance algorithms.

CONCLUSION

NT-proBNP is a valuable, non-invasive biomarker that strongly correlates with right ventricular dysfunction and remodeling in pediatric patients following congenital heart defect repair. It complements echocardiographic assessment and may serve as an early indicator of hemodynamic stress, guiding long-term monitoring and clinical decision-making. In pediatric patients following primary surgical correction of congenital heart defects, serum NT-proBNP levels offer prognostic information that complements echocardiographic assessment of right ventricular function. Their integration into follow-up protocols could enhance early detection of complications and optimize long-term outcomes.

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The Ability of Indirect Markers to Predict Cirrhosis Development in Hepatitis C

Sposobnost indirektnih markera u predikciji razvoja ciroze kod hepatitisa C

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ABSTRACT

Introduction: chronic hepatitis C is a disease with various clinical courses and outcomes. Knowledge of liver fibrosis stages is crucial for deciding whether treatment is necessary and when to start it. Liver biopsy is currently the gold standard for assessing the stage of fibrosis, but it is invasive, expensive, and patients are often reluctant to undergo it. Consequently, there is increasing interest in non-invasive methods for assessing fibrosis in hepatology. Objective: to determine whether non-invasive indirect markers can reliably identify patients who need antiviral treatment.Various markers were investigated and compared with histological findings of liver fibrosis in patients with chronic hepatitis. These markers included the AST/ALT ratio, APRI score, Forn's index, and FIB-4 index. Materials and Methods: the study included 60 patients with chronic hepatitis C confirmed by PCR analysis of HCV RNA, genotype determination, and liver fibrosis stage determined by histological analysis. Routine laboratory tests were performed on all patients to calculate the indirect markers. Patients were divided into five groups based on histological findings, and the stage of fibrosis was determined using the METAVIR grading system. Results: the most successful marker for predicting the development of cirrhosis is the APRI index, with a predictive significance level of (p =0.020. Conclusion: the most rational approach to using non-invasive markers for assessing fibrosis stage and predicting cirrhosis development is to combine indirect markers with Fibro Test or elastography, limiting the need for liver biopsy to cases where non-invasive fibrosis assessment is not possible (F2 and F3 stages) and when therapeutic treatment depends on histological results.

Keywords: indirect markers, liver fibrosis, liver biopsy

SAŽETAK

Uvod: kronični hepatitis C je bolest s različitim kliničkim tokovima i ishodima. Poznavanje stadija fibroze jetre ključno je za donošenje odluke je li liječenje potrebno i kada ga započeti. Biopsija jetre trenutno je zlatni standard za procjenu stadija fibroze, ali je invazivna i skupa, a pacijenti se nerado odlučuju za nju. Posljedično, raste interes za neinvazivne metode za procjenu fibroze u hepatologiji. Cilj: ispitati mogu li neinvazivni neizravni markeri pouzdano identificirati pacijente kojima je potrebno antivirusno liječenje. Ispitivani su različiti markeri i uspoređeni s histološkim nalazima fibroze jetre u bolesnika s kroničnim hepatitisom. Ti su markeri uključivali AST/ALTomjer, APRI index, Fornov indeks i FIB-4 indeks. Materijali i metode: istraživanjem je obuhvaćeno 60 bolesnika s kroničnim hepatitisom C potvrđenim PCR analizom HCV RNA, određivanjem genotipa i stadijem fibroze jetre utvrđenom histološkom analizom. Rutinski laboratorijski testovi provedeni su na svim pacijentima kako bi se izračunali neizravni markeri. Bolesnici su podijeljeni u pet skupina na temelju histološkog nalaza, a stadij fibroze određen je pomoću METAVIR klasifikacije. Rezultati: najuspješniji marker za predikciju razvoja ciroze je APRI indeks sa nivoom prediktone signinifikantnosti (p=0,020). Zaključak: najracionalniji pristup korištenju je neinvazivnih markera za procjenu stepena fibroze i predikciju razvoja ciroze je kombiniranje indirektnih markera sa Fibro testom ili elastografijom, ograničavajući potrebu za biopsijom jetre na slučajeve kad neinvazivna procjena fibroze nije moguća (F2 i F3 stadiji) i kad terapijsko liječenje ovisi o histološkim rezultatima.

Ključne riječi: indirektni markeri, fibroza jetre, biopsija jetre

INTRODUCTION

Chronic hepatitis C (CHC) represents a significant public health problem on a global scale. It is estimated that around 200 million people suffer from this disease in the world, and in certain geographical areas it has almost the characteristics of an epidemic. In most European countries the prevalence of infection is between 1-2% –.

Liver fibrosis is a dynamic process characterized by the excessive accumulation of extracellular matrix proteins in the liver, ultimately leading to the formation of scar tissue. In patients with hepatitis C, the progression of liver fibrosis is a critical determinant of the disease prognosis. Accurate assessment of liver fibrosis is essential for timely intervention and the management of patients with chronic hepatitis C (3,4,5,6).

While liver biopsy (LB) has traditionally been considered the gold standard for evaluating fibrosis, its invasive nature and associated risks have led to the development and utilization of non-invasive methods. Among these, indirect markers such as FIB-4 (Fibrosis-4), APRI (Aspartate Aminotransferase to Platelet Ratio Index),and various scores have emerged as valuable tools for assessing the degree of liver fibrosis . An ideal non-invasive marker should possess the following characteristics: specificity for liver fibrosis, provide a measure of activity and stage of fibrosis, not be influenced by other conditions or diseases, have a known half-life, have a known excretion pathway, be sensitive, and be reproducible (8.9).

The clinical assessment of patients with viral hepatitis C is based on a series of elements that should provide insight into the general condition of the patient, the course of the disease, the presence of complications of liver disease and extrahepatic manifestations of HCV infection, as well as other relevant diseases. However, two key elements in disease assessment are the status of viral infection and the histological stage of activity (10,11,12,13).

Therefore, surrogate markers of liver fibrosis may be considered appropriate for reducing the number of liver biopsy procedures in patients with hepatitis C.

AIM

The aim of this study is to examine which non-invasive markers, composed of simple and inexpensive diagnostic tests, provide the possibility of identifying patients in need of hepatitis C treatment and to investigate which of the indirect markers best differentiates clinically significant from insignificant fibrosis.

MATERIALS AND METHODS

Patients with chronic hepatitis C from single center (Clinical Center University of Sarajevo), characterized by the presence of HCV-RNA in blood serum, older than 18 years were included. The exclusion criteria were hepatitis B or human deficiency virus coinfection, self-reported excessive alcohol intake (>40g/day in men and >20g/day in women), chronic kidney disease and associated autoimmune disease.

The research was conducted based on the usual approach to the subject by collecting data through medical history, physical examination, laboratory tests, and histological analysis of liver tissue samples obtained by percutaneous liver biopsy.

During the examination, the physician completed a questio nnaire containing general information, information about the current disease with subjective symptoms, socio-epidemiological data, and information about previous illnesses. All patients underwent percutaneous liver biopsy.

Liver Biopsy

Percutaneous liver biopsies were performed under local anesthesia using a 16-G Menghini needle guided by ultrasound as a day-clinic hospitalization. All samples were fixed in a 10% neutral-buffered formalin solution and cut in 5mm thick sections.
Patients were divided into 5 groups according to histopathological findings, and the degree of fibrosis was determined according to the METAVIR system of grading:

1. F0 without fibrosis;
2. F1 portal fibrosis;
3. F2 periportal fibrosis or rare portal-portal septa;
4. F3 bridging fibrosis;
5. F4 definitive cirrhosis.

Data collection

Laboratory tests including complete blood count, serum HCV RNA concentration, HCV genotype, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), cholesterol, triglycerides, and serum iron level were performed for all patients.These parameters were used to calculate AST/ALT - AAR score, AST to platelet ratio index (APRI), Forn's index, and FIB-4 index.

- AST/ALT -AAR score is calculated using the formula:AST / ALT
- APRI is calculated using the formula:APRI = [AST (U/L) / upper limit of normal values (U/L)] × 100 / platelet count (10^9/L).
- FIB-4 index is calculated using the formula: FIB-4 = (age × AST (U/L)) / (platelet count (10^9/L) × ALT (U/L)).
- Forn's index is calculated as follows: Forn's Index = 7.811 - 3.131 × ln [platelet count (10^9/L)] + 0.781 × ln (GGT (IU/L)) + 3.467 × ln [age (years)] - 0.014 × [cholesterol (mg/dL)].

Statistical methods

Descriptive statistics of groups, as well as analysis and statistical processing within groups using appropriate statistical methods for the obtained parameters, were conducted.Variables such as AST/ALT -AAR score,AST to platelet ratio index (APRI), Forn's index, and FIB-4 index were analyzed. Logistic regression analysis was used to test associations among variables.A p-value of <0.05 on two-tailed t-test was considered statistically significant.

Ethical aspects of the study

The study was conducted in accordance with the latest revision of the Helsinki Declaration on the rights of patients involved in biomedical research and other documents regulating this area, as well as in accordance with local regulations. All patients voluntarily signed an Informed Consent Form before participating in the study.

RESULTS

The study included 60 patients (50 men and 10 women).

Descriptive analysis

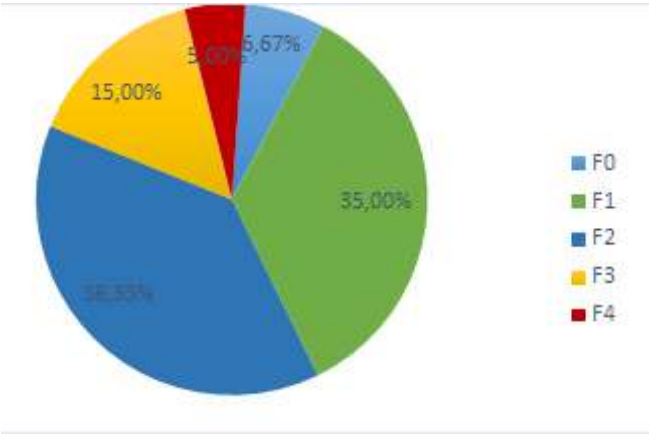

Figure 1 **Percentage of different fibrosis stages.**

Histopathological stage F0 by Metavir was demonstrated in 4 patients (6.6%), stage F1 in 21 patients, stage F2 in 23 patients (37.7%), stage F3 in 9 patients (14.8%), and stage F4 in 3 patients, which represent 4.9%.

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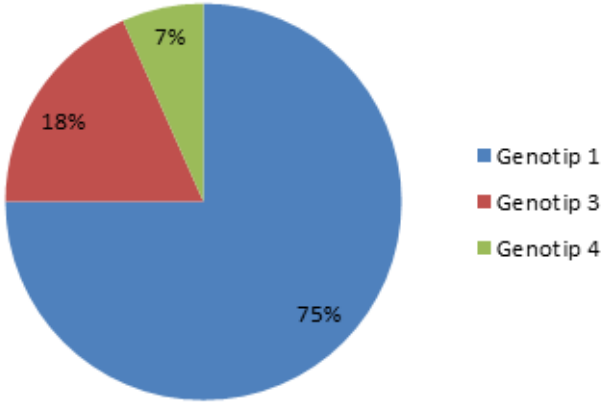

Figure 2 **Distribution of HCV genotype.**

The study showed that the most common genotype was type 1 (subtype 1b).

Table 1 **Descriptive analysis of measured parameters.**

	N	Minimum	Maximum	Mean	Std. Deviation
Age (years)	60	29	65	45.68	9.52
AST (U/L)	60	14	177	63.69	34.35
ALT (U/L)	60	23	377	111	72.86
GGT (U/L)	60	15	289	68.28	56.00
HOL (mg/dL)	60	2,4	6,9	4.38	0.97
TRC (10^9/L).	60	122	423	214.93	56.46
AAR	60	0.265	6.48	0.71	0.78
APRI	60	0.173	2.76	0.86	0.57
FIB-4 index	60	0.229	5.59	1.45	0.95
Forn's	60	4.769	11.15	7.29	1.35

Table 2 **Diagnostic accuracy of indirect markers in prediction of liver fibrosis development**

Model		Unstandardized Coefficients		Standardized Coefficients	p	Sig.
		B	Std. Error	Beta		
1	(Const.)	.179	.555		.322	.749
	AAR	-.138	.169	-.218	-.818	.417
	APRI	.469	.196	.547	2.399	.020
	FIB-4 index	-.049	.229	-.096	-.216	.830
	Forn's	.024	.091	.065	.260	.795

This table presents the results of a multiple linear regression analysis evaluating the influence of four predictors: AAR, APRI, FIB-4 Index, and Forn's Index on the dependent variable.

Unstandardized Coefficients (B): Indicate the change in the dependent variable for a one unit change in the predictor, holding all other variables constant. Standardized Coefficients (Beta): Show the relative strength of each predictor on a standardized scale, allowing for comparison between variables measured on different scales. Sig. (p-value): The p-value tests the null hypothesis that the coefficient is equal to zero. The Sig. (p-value) indicates whether the predictor is statistically significant (typically $p < 0.05$).

Interpretation: APRI is the only statistically significant predictor in this model ($B = 0.469$, $p = 0.020$), suggesting a meaningful positive association with the dependent variable. A one-unit increase in APRI is associated with an increase of 0.469 in the dependent variable. AAR ($p = 0.417$), FIB-4 Index ($p = 0.830$), and Forn's Index ($p = 0.795$) are not statistically significant predictors, indicating that they do not have a meaningful contribution to the model in this context. The constant (intercept) is not statistically significant ($p = 0.749$), and represents the expected value of the dependent variable when all predictors are zero.

Among the four evaluated markers, APRI stands out as the only significant predictor in the regression model. This suggests that APRI may be the most useful index for predicting the liver fibrosis/cirrhosis.

DISCUSSION

In our study, which included 60 patients (50 men and 10 women) treated at our clinic for hepatitis C virus infection, the mean age was 45.68 years, with the youngest patient being 29 years old and the oldest 65 years old. The age at the time of infection acquisition is a crucial factor determining disease progression. The lowest risk of progression is observed in individuals infected at younger than 20 years of age, intermediate risk in those aged 20-40 years, and the highest risk in those over 40 or 50 years of age (6,7,14,15).

Out of 60 subjects, histopathological stage F0 by Metavir was demonstrated in 4 patients (6.6%), stage F1 in 21 patients, stage F2 in 23 patients (37.7%), stage F3 in 9 patients (14.8%), and stage F4 in 3 patients, which represent 4.9% (Figure 1).

With such a distribution of fibrosis stages, as found in our subjects, with the highest percentage of F2 fibrosis stage, lower success in assessing fibrosis non-invasively can be expected. Most published studies show that the F2 stage is the most difficult to correctly classify with non-invasive fibrosis markers (16,17,18, 20,21,22).

The study showed that the most common genotype was type 1 (subtype 1b) (Figure 2). The aim of the study was to compare the success of indirect markers, AAR score, APRI score, Forn's index, and FIB-4 index, according to their ability to predict the development of cirrhosis. We investigated diagnostic accuracy of indirect markers: AST/ALT - AAR score, AST to "platelet ratio index" - APRI score, Forn's index, and FIB-4 index in prediction of liver fibrosis development The results of our study suggests that APRI, with statistical significance for prediction at the p-level 0,020, may be the most useful index for predicting the liver fibrosis/cirrhosis (Table 3). Non-invasive serological and elastography methods can be reliably used to assess fibrosis severity, with greater reliability for detecting cirrhosis compared to significant fibrosis (F≥2). In a study conducted on 575 patients. Furthermore, both APRI and FIB-4 scores reduce the need for transient elastography (23).

Other studies have also shown that APRI and FIB-4 are sensitive and reliable non-invasive diagnostic tools, and that they are also useful markers for excluding the presence of liver cirrhosis.

By combining two non-invasive methods, it is possible to assess fibrosis stage (especially F≥2) with greater reliability and thus avoid liver biopsy in up to 77% of patients with chronic hepatitis C (24,25). FIB-4 proved to be more effective than APRI in the evaluation of liver fibrosis in patients with HCV infection. Specifically, in patients with F4 fibrosis, the AUC for FIB-4 was 0.73, compared to 0.70 for APRI (22). Likewise, conclusion from Turkish non-interventional prospective observational study, presented that the use of Fibro test, FIB-4, APRI, AP index and Forn's index exhibit good diagnostic performance for determining liver fibrosis in CHC patients, and the use of at least two tests together will increase their diagnostic value still further. Data from 182 patients with baseline liver biopsy were suitable for analysis. One hundred and twenty patients (65.9%) had F0-F1 fibrosis and 62 patients (34.1%) had F2-F4 fibrosis. APRI 0.732 area under the curve (AUC) indicated advanced fibrosis with 69% sensitivity and 77% specificity. FIB-4 0.732 AUC and Fibro Test 0.715 AUC indicated advanced fibrosis with 69% and 78.4% sensitivity, and 75% and 71.4% specificity, respectively. The combined use of tests also led to an increase in AUC and specificity. Combinations of Fibro Test with APRI and/or FIB-4, and FIB-4 with APRI were optimal for the evaluation of liver fibrosis (25).

CONCLUSION

This study highlights the potential of using non-invasive biomarkers for predicting the development of cirrhosis in patients with hepatitis C. The APRI index demonstrated the best predictive ability. However, the use of these biomarkers in clinical practice remains somewhat limited due to the variability in results and the inability of any single test to definitively diagnose liver fibrosis or cirrhosis. Therefore, these tests are usually employed as part of a broader fibrosis assessment strategy, alongside clinical evaluation and other diagnostic tools. In perspective, the use of non-invasive markers of fibrosis in clinical practice is expected to increase as their utility becomes better defined for specific patient categories.

LIMITATION

Limitation of this study was the relatively small sample size, particularly the low number of patients with advanced liver cirrhosis. This may impact the reliability and interpretation of the results and limits the strength of the conclusions that can be drawn. Future studies with larger and more diverse patient populations are needed to validate these findings and refine the clinical application of non-invasive fibrosis markers.

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The Comorbidity of Personality Disorders with Bipolar Affective Disorder Type I

Povezanost poremećaja ličnosti sa bipolalrnim afektivnim poremećajem Tip I

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ABSTRACT

The comorbidity of personality disorders with bipolar affective disorder represents a complex phenomenon in the field of mental health. Bipolar affective disorder, known for its cyclical episodes of mania and depression, can be further complicated by the presence of personality disorders. Personality disorders are characterized by deep and enduring patterns of behavior, thinking and functioning that often interfere with interpersonal relationships and daily functioning. When these two disorders co-occur, symptoms can be more pronounced, and treatment becomes more complex. Individuals with this comorbidity often experience more severe episodes of mania and depression, a higher risk of suicide, and difficulties in maintaining stable interpersonal relationships. To successfully address this challenge, it is crucial to tailor the therapeutic approach to the needs of each individual. This includes a combination of pharmacotherapy, psychotherapy, and psychosocial support. Additionally, it is important to continuously monitor and adjust treatment to ensure that patients receive optimal support and improve their quality of life.

Keywords: bipolar affective disorder, personality disorder, comorbidity

SAŽETAK

Povezanost poremećaja ličnosti s bipolarnim afektivnim poremećajem predstavlja složen fenomen u području mentalnog zdravlja. Bipolarni afektivni poremećaj, poznat po cikličkim epizodama manije i depresije, može biti dodatno kompliciran prisustvom poremećaja ličnosti. Poremećaj ličnosti karakterišu duboki i trajni obrasci ponašanja, mišljenja i funkcionisanja, koji često ometaju međuljudske odnose i svakodnevno funkcionisanje. Kada se ova dva poremećaja udruže, simptomi mogu biti izraženiji, a dijagnostika i terapija složenija, što utiče na tok bolesti i ishode liječenja. Osobe s povezanošću ova dva poremećaja često imaju teže epizode manije i depresije, veći rizik od suicida, te poteškoće u održavanju stabilnih interpersonalnih odnosa. Kako bi se uspješno nosili s ovim izazovom, ključno je prilagoditi terapijski pristup potrebama svakog pojedinca. To uključuje kombinaciju farmakoterapije, psihoterapije i psihosocijalne podrške. Osim toga, važno je kontinuirano pratiti i prilagođavati terapiju kako bi se osiguralo da pacijenti dobiju optimalnu podršku i poboljšaju kvalitet svog života.

Ključne riječi: bipolarni poremećaj, poremećaj ličnosti, komorbiditet

INTRODUCTION

Every individual has a unique personality, a set of traits manifested through characteristic ways of thinking, relating to others, and behaving. Personality is formed through a combination of genetic predispositions, childhood experiences, and social influences. It affects all aspects of life from interpersonal relationships to how we cope with stress and challenges. Individuals with personality disorders often suffer from other psychiatric disorders as well (1). Bipolar affective disorder type I, characterized by episodes of mania that may be followed by depressive episodes, is complex and challenging to diagnose and treat. The coexistence of a personality disorder further complicates the clinical picture, requiring a deeper understanding and a more careful therapeutic approach.

AIM

Personality disorders represent a complex group of mental disorders characterized by persistent, inflexible, and maladaptive patterns of thinking, functioning, and behavior. These patterns significantly deviate from cultural expectations and cause substantial impairments in occupational, social, and other life domains.

MATERIALS AND METHODS

The pathogenesis of personality disorders is multifactorial, involving biological, genetic, psychological, and social factors. Understanding these disorders requires a comprehensive approach, incorporating all aspects to develop effective treatment strategies and support systems. Personality disorders are often comorbid with other psychiatric conditions, complicating clinical presentation, diagnosis, and treatment, and thus demanding interdisciplinary collaboration in patients' care (1). The prevalence of personality disorders in the general population ranges from 10% to 13%. When assessing individual functioning, it is essential to consider the patient's ethnic, cultural, and social background. Personality disorders should not be confused with adjustment difficulties after immigration or with cultural habits, political beliefs, or religious characteristics. Diagnosis in children or adolescents should be made only if maladaptive traits are pervasive, long-standing, and not associated with a particular developmental stage or transient episode. The prevalence of the three personality disorder clusters (A, B, and C) is 3.6%, 1.5%, and 2.7%, respectively. This classification helps organize and understand different types of personality disorders, facilitating diagnosis and treatment approaches (2).

Diagnosis of Personality Disorders

There are two main diagnostic approaches: categorical approach, as found in ICD-10 and Section II of DSM-5, defines personality disorders as qualitatively distinct syndromes. Dimensional approach, also utilized in DSM-5, emphasizes functional impairment and pathological personality traits. The main drawback of the categorical approach is its limited specificity, as patients often meet criteria for multiple personality disorders. The alternative DSM-5 model provides a more precise diagnosis by focusing on functional impairment and trait pathology (1).

Treatment of Personality Disorders

For Cluster A disorders (paranoid, schizoid, schizotypal), group therapy may be inappropriate due to mistrust. Instead, individual social skills training and second-generation antipsychotics are preferred. Cluster B disorders (antisocial, borderline, histrionic, narcissistic) may benefit from both group and individual therapy. Cluster C disorders (avoidant, dependent, obsessive-compulsive) respond well to cognitive-behavioral therapy, especially in addressing assertiveness, autonomy, and anxiety, with SSRIs often prescribed for underlying anxiety. Supportive psychotherapy, assertiveness training, social skills development, and psychodynamic therapy are effective for avoidant personality disorder. Obsessive-compulsive personality disorder often responds well to psychoanalytic psychotherapy (2).

Bipolar Affective Disorder Type I

Bipolar affective disorder is a severe mood disorder characterized by alternating episodes of depression and (hypo) mania, usually separated by periods of normal mood and functioning (3). The lifetime prevalence of bipolar affective disorder type I is approximately 0.6%, with over 70% of individuals exhibiting symptoms before age 25. Biochemical and pharmacological research supports the catecholamine hypothesis, suggesting mania results from excess and depression from deficiency of catecholamines. Additionally, serotonin hypotheses point to low serotonergic function contributing to both manic and depressive states via dysregulated suppression of other neurotransmitters. Neuroanatomical and imaging studies implicate lesions in the frontal and temporal lobes, with left-sided lesions more associated with depression and right-sided with mania. However, patterns may reverse in posterior regions. While no consistent abnormalities have been found via CT, enlarged ventricles are suspected (4).

Diagnosis of Bipolar Affective Disorder Type I

A diagnosis requires at least one manic episode, defined by a distinct period of persistently elevated or irritable mood and increased activity or energy lasting at least seven days, or requiring hospitalization. During a manic episode, three or more (or four if the mood is irritable) of the following symptoms must be present: inflated self-esteem or grandiosity, decreased need for sleep, excessive talking or pressured speech, flight of ideas or racing thoughts, distractibility, increased goal-directed activity or psychomotor agitation, risky behavior (e.g., spending sprees, sexual indiscretions, risky investments) (5).

Treatment of Bipolar Affective Disorder Type I

Treatment is phase-specific and requires precise pharmacological intervention to improve outcomes and reduce relapse. Lithium is well-documented as a mood stabilizer, effective in treating acute mania, depression, and preventing recurrences. Anticonvulsants such as valproate and carbamazepine are also effective in acute mania and long-term maintenance, although evidence for acute depression is limited compared to lithium (4).

RESULTS

Comorbidity of Personality Disorders and Bipolar Affective Disorder Type I

Personality disorders are commonly comorbid with bipolar affective disorder, affecting up to 40–50% of patients (6). This comorbidity significantly influences disease course and outcomes. These patients often show more severe mood symptoms, reduced social functioning, and higher rates of suicidal ideation and behavior (7). They are also hospitalized more frequently and have more difficulty achieving symptomatic recovery. Cluster B (borderline, narcissistic, antisocial, histrionic) and Cluster C (avoidant, dependent, obsessive-compulsive) disorders are more commonly comorbid than Cluster A. Borderline Personality Disorder (BPD) and bipolar affective disorder type I are among the most frequently diagnosed psychiatric conditions, both associated with high morbidity and suicide risk. Despite symptom overlap, BPD is marked by identity diffusion, while bipolar disorder features identity conflict. Research confirms high rates of comorbidity (~21%), with male gender and older age predicting lower comorbidity (8). Narcissistic Personality Disorder (NPD) shares features with mania such as grandiosity and goal-directed behavior. NPD is associated with worse clinical outcomes, even during remission. Both may reflect different expressions of grandiosity and emotional vulnerability, potentially existing on a continuum (9). Histrionic Personality Disorder (HPD) and bipolar affective disorder type I share traits such as impulsivity and emotional reactivity. Comorbidity leads to more severe clinical presentations, greater mood instability, and lower quality of life (10). Antisocial Personality Disorder (ASPD) is more prevalent in bipolar affective disorder type I (up to 4.1%). Comorbidity results in earlier onset, more severe episodes, increased aggression, higher suicide risk, and substance abuse, leading to worse prognosis (2). Anxiety disorders are also common in bipolar disorder, with up to 50% experiencing lifetime comorbidity. Anxiety may persist even in euthymic states and contributes to more severe symptoms and worse treatment outcomes (11).

DISCUSSION

This study aimed to explore the relationship between personality disorders and bipolar affective disorder type I, and how this comorbidity affects clinical presentation and treatment outcomes. Evidence shows high prevalence of personality disorders, particularly Cluster B, among patients with bipolar affective disorder type I. These patients exhibit more severe symptoms, frequent episodes, and poorer psychosocial adjustment, ultimately affecting overall quality of life. Effective treatment of these patients requires a comprehensive, multidisciplinary approach, including family and community support. By better understanding the psychological complexity of these disorders including internal conflict, defense mechanisms, and the biological and psychosocial underpinnings clinicians can develop more effective treatment protocols. A national observational study from Japan further supports the link between personality disorder diagnosis and long-term remission in bipolar patients (12).

CONCLUSION

The comorbidity of personality disorders and bipolar affective disorder type I significantly affect symptom severity, disease progression, and complicate accurate diagnosis. Patients with comorbid conditions experience more intense manic and depressive episodes, poorer functional outcomes, and greater difficulty in achieving remission. A tailored treatment plan that includes pharmacotherapy and psychotherapy, alongside ongoing monitoring and patient education, is essential for improving patient outcomes and quality of life.

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Alpha-1 antitrypsin deficiency - an underrecognized genetic disorder

Deficit alfa-1 antitripsina - nedovoljno prepoznat genetski poremećaj

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ABSTRACT

Alpha-1 antitrypsin (AAT) deficiency is a clinically under recognized inherited disorder affecting the lungs, liver, and rarely skin. Aim: to highlight clinically unrecognized severe Alpha-1 antitrypsin (AAT) deficiency in those with no clinical manifestations and in those with disease in whom the underlying AAT deficiency has not been recognized. Methods: A comprehensive review of the available medical literature was conducted on the prevalence of common unrecognized severe AAT deficiency. The pathogenesis, genetics of AAT with the most common mutations, risk factors, clinical manifestations, diagnostic methods, and recommendations for treatment were investigated. Topic review: AAT is a protease inhibitor (Pi) of the proteolytic enzyme elastase and also of the proteases trypsin, chymotrypsin, and thrombin. Emphysema in AAT deficiency (AATD) results from an imbalance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which is synthesized in hepatocytes and protects against proteolytic degradation of elastin. AATD might be interpreted as a common mechanism with different clinical manifestations and frequent overlap among chronic respiratory disorders, such as asthma, COPD and bronchiectasis, in which the underlying AAT deficiency has not been recognized. The diagnosis of severe deficiency of AAT is confirmed by demonstrating a serum level below 11 micromol/L in combination with a severe deficient phenotype, or genotype. Smoking cessation and augmentation therapy consisting of intravenous therapy with exogenous AAT protein harvested from pooled blood products, are used in patients with emphysema due to AAT deficiency. Lung transplantation is reserved for patients with advanced emphysema due to severe AAT deficiency. Conclusion: all adults with persistent airflow obstruction on spirometry should be tested for AATD. Additional features that should lead clinicians to test for AATD include emphysema in a young and a non-smoker individual, adult-onset asthma as well as a family history of emphysema and/or liver disease.

Keywords: persistent airflow obstruction, lung emphysema, alpha-1 antitrypsin deficiency

SAŽETAK

Deficijencija alfa-1 antitripsina (AATD) je klinički nedovoljno prepoznata nasljedna bolest koja pogađa pluća, jetru i rijetko kožu. Cilj: istaknuti klinički neprepoznatu tešku deficijenciju alfa-1 antitripsina (AAT) kod osoba bez kliničkih manifestacija i kod osoba s bolešću kod kojih osnovni nedostatak AAT nije prepoznat. Metode: Izvršen je opsežan pregled dostupne medicinske literature o prevalenciji često neprepoznatog teškog deficita AAT-a. Istraženi su patogeneza, genetika AAT-a s najčešćim mutacijama, faktori rizika, kliničke manifestacije, dijagnostičke metode i preporuke za liječenje. Pregled teme: AAT je inhibitor proteaze (Pi) proteolitičkog enzima elastaze, kao i proteaza tripsina, himotripsina i trombina. Emfizem kod AATD nastaje zbog neravnoteže između neutrofilne elastaze u plućima, koja uništava elastin, i inhibitora elastaze AAT, koji se sintetizira u hepatocitima i štiti od proteolitičke razgradnje elastina. AATD se može tumačiti kao zajednički mehanizam s različitim kliničkim manifestacijama i čestim preklapanjem među hroničnim respiratornim bolestima, poput astme, HOPB-a i bronhiektazija, kod kojih osnovni nedostatak AAT nije prepoznat. Dijagnoza teškog nedostatka AAT-a potvrđuje se nivoom u serumu ispod 11 mikromola/L u kombinaciji s teško deficijentnim fenotipom ili genotipom. Prestanak pušenja i augmentacijska terapija, koja se sastoji od intravenske terapije egzogenim AAT proteinom prikupljenim iz krvnih produkata, primjenjuju se kod pacijenata s emfizemom uzrokovanim nedostatkom AAT-a. Transplantacija pluća je rezervirana za pacijente s uznapredovalim emfizemom uzrokovanim teškim nedostatkom AAT-a. Zaključak: sve odrasle osobe s perzistentnom opstrukcijom protoka zraka na spirometriji trebaju biti testirane na AATD. Dodatne karakteristike koje bi trebale navesti kliničare na testiranje na AATD, uključuju emfizem kod mladih osoba nepušača, astmu s početkom u odrasloj dobi, kao i porodičnu anamnezu emfizema i/ili bolesti jetre.

Ključne riječi: perzistentna opstrukcija protoka zraka, emfizem pluća, nedostatak alfa-1 antitripsina

INTRODUCTION

Alpha-1 antitrypsin (AAT) deficiency is a clinically under recognized inherited disorder affecting the lungs, liver, and rarely skin. In the lungs, AAT deficiency causes chronic obstructive pulmonary disease (i.e., emphysema and bronchiectasis). The prevalence is from 1 in 3500 to 1 in 1500 and severe deficiency is estimated to be present in approximately 1 in 200 patients with chronic obstructive pulmonary disease (COPD) (1,2,3).

AIM

The aim of the study was to highlight clinically unrecognized severe Alpha-1 antitrypsin (AAT) deficiency in those with no clinical manifestations and in those with disease in whom the underlying AAT deficiency has not been recognized.

METHODS

An extensive review of the available medical literature was conducted on the prevalence of common unrecognized severe AAT deficiency. The pathogenesis, genetics of AAT with the most common mutations, risk factors, clinical manifestations, diagnostic methods and recommendations for treatment were investigated.

TOPIC REVIEW

AAT is a protease inhibitor (Pi) of the proteolytic enzyme elastase and also of the proteases trypsin, chymotrypsin, and thrombin. It is part of a larger family of structurally unique serine protease inhibitors, referred to as SERPINS (4). Emphysema in AAT deficiency (AATD) results from an imbalance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which is synthesized in hepatocytes and protects against proteolytic degradation of elastin (5) (Figure 1,2). AATD might be interpreted as a common mechanism with different clinical manifestations and frequent overlap among chronic respiratory disorders inhibitors (6,7) (Figure 3,4).

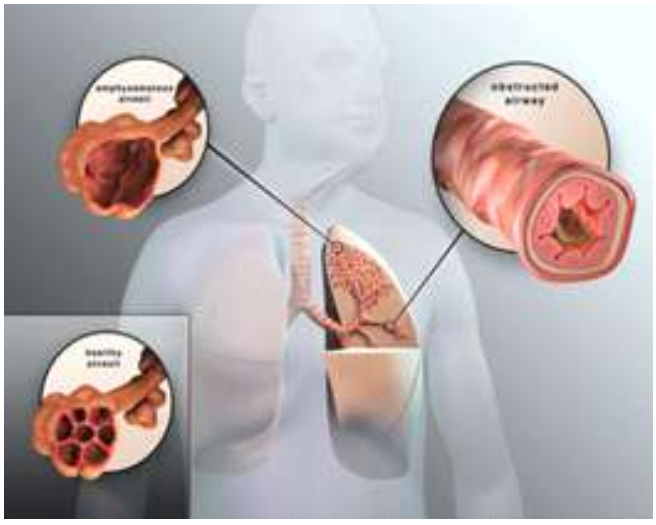
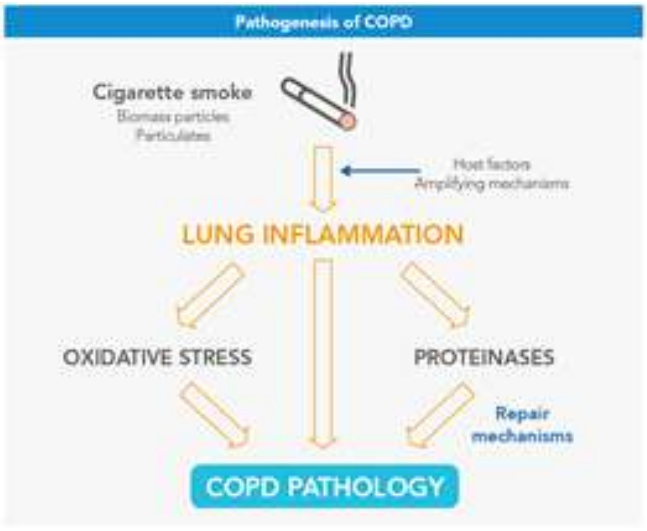


Figure 1 **The presentation of healthy alveoli, obstructed airways, and emphysematous alveoli.**



Adapted from Alexandre BM and Penque D. J Aller Ther 2012; S7: 003

Figure 2 **Pathogenesis of COPD.**

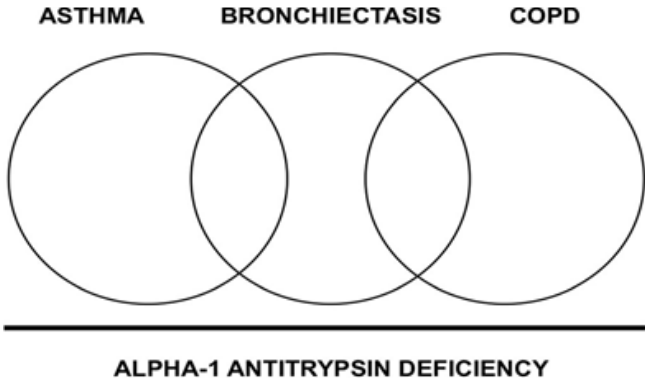


Figure 3 **AATD might be interpreted as a common mecha nism with different clinical manifestations and frequent overlap among chronic respiratory disorders.**
(Source: Gramegna et al. Multidisciplinary Respiratory Medicine 2018.)

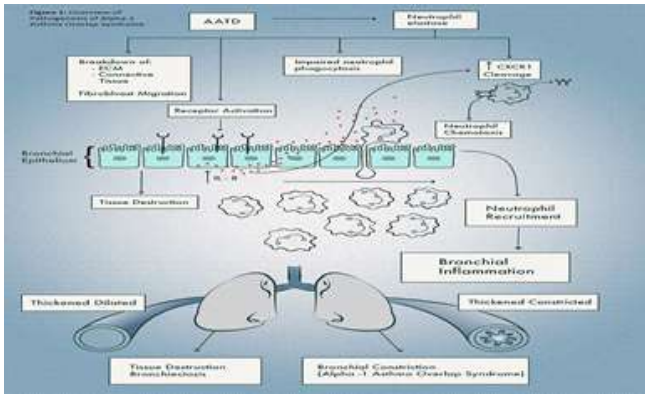


Figure 4 **Overview of Pathogenesis of Alpha-1 Asthma Overlap Syndrome.**
(Source: Manuel Izquierdo et al. Current Allergy and Asthma Reports, 2022.)

AAT genetics

AATD is inherited by autosomal co-dominant trans mission. The gene that encodes AAT is called SERPINA1 (OMIM +107400) and is located on the long arm of chromosome 14. PI*ZZ denotes homozygosity for the Z allele, the most common mutation in the SERPINA1 gene that leads to AAT deficiency (4,5).

The liver disease results from the accumulation within the hepatocyte of unsecreted variant AAT protein.

Only those genotypes associated with pathologic polymeri zation of AAT within the endoplasmic reticulum of hepatocytes (e.g., PI*ZZ type AATD) produce disease (fibrogenesis, hepatocarcinogenesis) (8,9,10).

Risk factors for lungs disease and clinical presentation

- Individuals with phenotypes associated with AAT levels below the protective threshold of 11 micromol/L (approximately 57 mg/dL using nephelometry and 80 mg/dL by older radial immunodiffusion methods) are considered to have severe deficiency of AAT and are at risk for emphysema (1,11).
- Risk factors for emphysema include cigarette smoking, dusty occupational exposure, a parental history of COPD, and a personal history of asthma, chronic bronchitis or pneumonia. Approximately 90 percent of subjects with severe deficiency of AAT who smoke will develop radiographic emphysema, compared with 65 percent of nonsmokers.
- Emphysema associated with severe deficiency - onset at a younger age and a basilar-predominant pattern
- Upper lobe predominant pattern of emphysema (one third) that is more characteristic of non-AAT deficient COPD.
- Spontaneous secondary pneumothorax
- Bronchiectasis (12,13,14)

Clinical presentation of extrapulmonary disease

Patients with at-risk phenotypes for liver disease (eg, Z, S [iiyama], M[malton]) may develop adult-onset chronic hepatitis, cirrhosis, or hepatocellular carcinoma (Figure 7). Other rarer extrapulmonary manifestations of AATD include panniculitis (hot, painful, red nodules or plaques characteristically on the thigh or buttocks) (Figure 5,6). Vasculitis, inflammatory bowel disease, intracranial and intra-abdominal aneurysms, fibromuscular dysplasia and glomerulonephritis could be possible extrapulmonary manifestations of the disease (3,15).

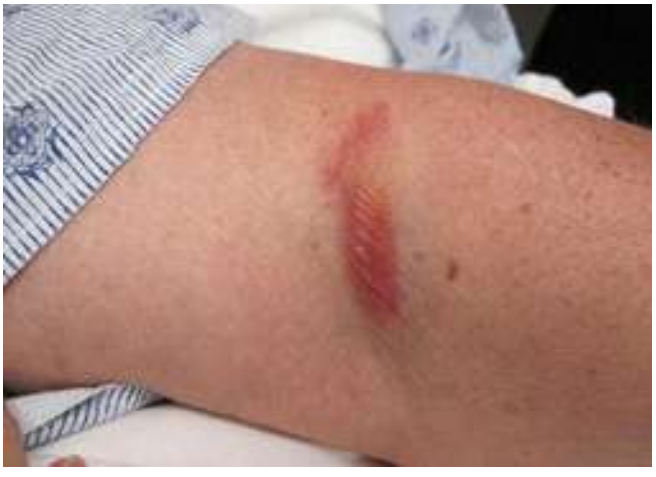


Figure 5 **Edematous inflammatory plaque on the proximal left arm (panniculitis as extrapulmonary manifestations of AATD).** (Source: Cutis. 2014;93:303-306)

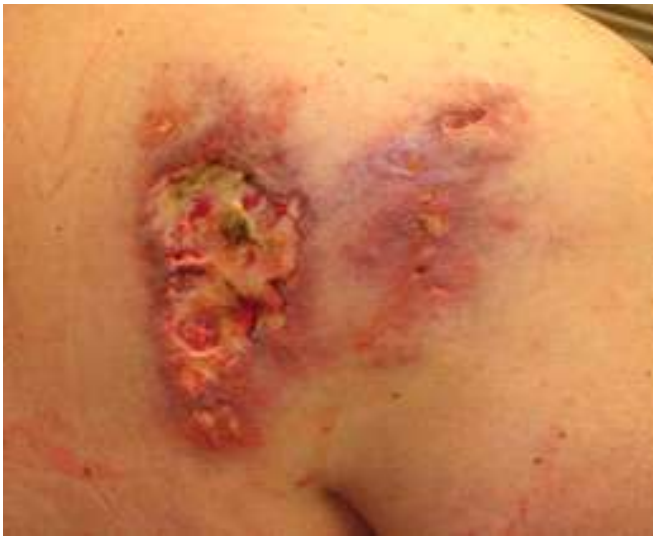


Figure 6 **Ulcerated lesion on the posterior aspect of the right shoulder resembling pyoderma gangrenosum (panniculitis in AATD).** (Source: Cutis. 2014;93:303-306)

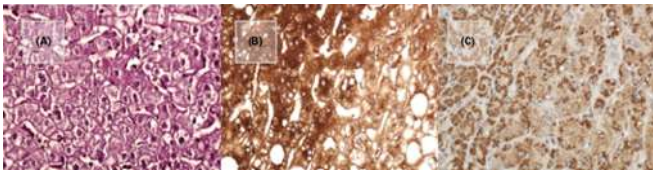


Figure 7 **Liver damage in patients with α1-antitrypsin deficiency.**

A Periodic acid Schiff diastase (PAS-d) staining showing intracytoplasmic accumulation of PAS-d-resistant material
B Immunohistochemical staining of the case patient's hepatocytes
C Control immunohistochemical staining of a known ∫1antitrypsin–deficient patient

(Source: Rider NL, Craig TJ. Liver enzyme elevation and normal pulmonary function in an adult with a declining forced expiratory volume in 1 second. Allergy Asthma Proc. 2008;29:345-348)

EVALUATION AND DIAGNOSIS

All adults with persistent airflow obstruction on spirometry should be tested for AATD (16,17)

Additional features that should lead clinicians to test for AATD include (1)

- Emphysema in a young individual (e.g., age ≤45 years)
- Emphysema in a nonsmoker or minimal smoker
- Emphysema characterized by predominant basilar changes on the chest radiograph
- A family history of emphysema and/or liver disease
- Adult-onset asthma (when airflow obstruction fails to normalize after bronchodilators)
- Clinical findings or history of panniculitis
- Clinical findings or history of unexplained chronic liver disease

Diagnosis

The diagnosis of severe deficiency of AAT is confirmed by demonstrating a serum level below 11 micromol/L (approximately 57 mg/dL by nephelometry) in combination with a severe deficient phenotype, generally determined by isoelectric focusing, or genotype, assessed by testing for the most common deficient alleles (ie, S, Z, I, F) (13).

AAT levels can determine who should have further tests with a high sensitivity and specificity and should be measured with CRP.AAT and C-reactive proteini (CRP) levels are measured concurrently: this may identify patients with an inflammatory state potentially affecting AAT levels (1,18).

Uncommon genotype that can produce normal serum AAT levels but pose emphysema risk is PI*FF, in which the F allele is quantitatively normal but functionally impaired in binding neutrophil elastase (13).

Laboratory testing

Isoelectric focusing – Isoelectric focusing is the gold standard blood test for identifying AAT variant proteins, which migrate differently under isoelectric focusing. It is performed less often, but is still sometimes useful for rare variants (eg, F, I, P) (1,15).

Genotyping is performed by identifying specific alleles in DNA (by PCR technology or by gene sequencing).The preferred approach is to obtain simultaneous testing of the serum AAT level by nephelometry and targeted genotyping for the most common variants (17). Initial genotyping would also be acceptable (19).

Gene sequencing is prudent when the serum level and the reported genotype seem discordant or when the patient's clinical features cannot be explained by the reported genotype. It is important to review the genetic origins of samples when evaluating patients who have received a liver or hematopoietic cell transplant (HCT), particularly when there is discordance between tests (20).

Pulmonary function testing and Imaging

Spirometry before and after bronchodilator, lung diffusion capacity (DLCO) must be performed (17).

If DLCO is below normal or if the patient reports exertional dyspnea, a six-minute walk test is often obtained.

Lung function is often characterized by earlier reduction in gas transfer and FEV1 often declines later in disease progression. Patients with airflow limitation and FEV_1 <80 percent of predicted post-bronchodilator are candidates for augmentation therapy (15).

Chest imaging is used to determine the pattern and extent of emphysema in AATD even in normal lung function. The "classic" pattern of emphysema in AATD is basilar predominant bullae although the apical predominant emphysema may be seen (17) (Figure 8).

CT scanning predicts all-cause mortality in ∫1-antitrypsin defici ency and appears to be superior to lung function parameters, especially FEV_1 (21).

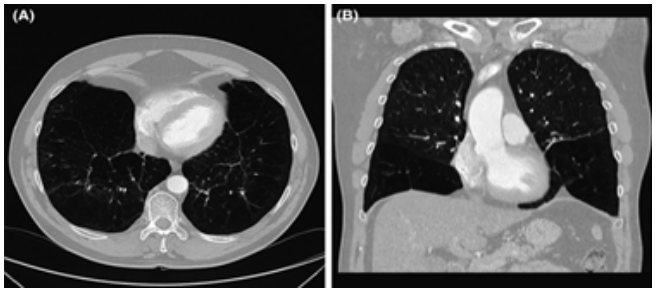


Figure 8 **CT scans showing extensive emphysematous damage to the lungs A-Axial plane of thorax; B-Coronal plane of thorax.**
(Source: Craig TJ et al. Allergy.2018 Nov; 73(11): 2110–2121)

MONITORING ASYMPTOMATIC PATIENTS

For patients with no respiratory symptoms and a normal baseline spirometry (ie, forced expiratory volume in one second [FEV1] ≥80 percent of predicted), spirometry is typically repeated when symptoms change or at 6- to 12-month intervals.An unexplained decrease in the postbronchodilator FEV1 to less than 80 percent predicted is an indication to initiate augmentation therapy (1,17).

Supportive therapy is applied in the patients with emphysema due to AAT deficiency following the usual guidelines for COPD (pulmonary rehabilitation, nutritional support, supplemental oxygen, preventive vaccination - influenza and pneumococcal vaccines and prompt treatment of lower respiratory tract infections). Pharmacologic therapy for emphysema is administered as well.

Management of liver complications is also important (liver biochemistry, ultrasound) (ATS and ERS suggest monitoring liver function annually) (1,22). Genetic counselling, smoking cessation are performed as well. Cigarette smoking is known to accelerate progression of lung disease in AAT deficiency.

Augmentation therapy (augments the circulatory concentrations of AAT serum levels above a proposed "protective threshold") consists of intravenous therapy with exogenous AAT protein harvested from pooled blood products (16,22).

How should we care for patients heterozygous for AATD?

The frequency of SZ individuals is much lower than that of MZ individuals and serum AAT levels are reduced to 40% of those found in MM individuals. The risk of COPD is increased in SZ individuals compared to MM counterparts and more so in cigarette smokers.

- Smoking cessation should be strongly encouraged in heterozygous for AATD but regular follow up is not advised.
- In COPD patients heterozygous for AATD, usual COPD care is advised (3,23).
- Suarez-Lorenzo et al. studied the ∫1-AT distribution in an allergic asthmatic population and reported that 22.4% of asthmatic patients had at least one mutated allele (S or Z) (24).

TREATMENT

Intravenous augmentation therapy

Patient selection

- AAT deficient patients in never or ex-smokers, age 18 or older with an AAT genetic variant consistent with severe AAT deficiency, and evidence of airflow limitation (FEV1 30 to 65 percent predicted) (Grade 2B).
- Nonsmoking adult patients with severe AAT deficiency and FEV1 >65 percent predicted who also demonstrate a declining FEV1 (≥100 mL/year decline) or radiographic evidence of significant emphysema (Grade 2C).
- Indications for use of AAT augmentation for those with FEV1 <30 percent predicted or FEV1 >65 percent predicted have not been uniformly agreed upon.
- Dose – For the majority of patients receiving AAT augmentation, pooled human AAT is administered intravenously 60 mg/kg actual body weight, per week (15,16).
  Thoracic Society of Australia and New Zealand recommends that augmentation therapy could be considered in non-smoking patients with AATD (conditional recommendation and low-quality evidence (3).

Lung volume reduction

Small studies of lung volume reduction surgery (LVRS) in AAT deficient patients suggest caution in advising surgery for those with severe AAT (1).
-Lung volume reduction surgery - LVRS (also called reduction pneumoplasty or bilateral pneumectomy) is a surgical technique that entails reducing the lung volume by wedge excision of emphysematous tissue. Basal predominance of emphysema or diffuse emphysema with a low diffusing capacity for carbon monoxide (DLCO) may make LVRS more difficult in AAT deficient patients (17). LVRS has not been shown to improve survival or substantially improve lung function compared with medical therapy (3,15).

LVRS is not advised for AATD due to a lack of evidence supporting its use."

Bronchoscopic lung volume reduction – Based on limited data from retrospective case series and subgroup analyses of clinical trials, severe AAT patients who qualify for bLVR with endobronchial valves appear to demonstrate similar improvements in forced expiratory volume in one second (FEV1), dyspnea, and quality-of-life and similar risk of complications (eg, pneumothorax, chronic obstructive pulmonary disease [COPD] exacerbation) as COPD patients without severe AAT (25,26).

Lung transplantation

Advances in solid organ transplantation have made lung (and liver) transplantation available as therapeutic options for AAT-deficient patients.

Lung transplantation (LT) is reserved for patients with advanced emphysema due to severe AAT deficiency. There is the possibility of underlying liver disease for potential lung transplant candidates with AAT deficiency.

In a single institution study, a pretransplant liver biopsy was performed in all lung transplant candidates with Pi*ZZ emphysema. Chronic liver disease was noted on biopsy in 20 of 23 patients and two patients met criteria for severe liver disease. Two patients with severe liver disease were asymptomatic and had normal liver function tests; one had an abnormal ultrasound. Seventeen patients underwent lung transplantation, and no evidence of decompensation of liver disease was noted; two with severe liver disease were not listed for transplant (27).

To evaluate for concomitant occult liver disease liver function tests and elastography are assessed prior to listing a patient for lung transplantation, but not routinely performing liver biopsy (28).

Outcomes of lung transplantation

Observational studies suggest that lung transplantation in patients with advanced lung disease due to AAT deficiency has a comparable survival to lung transplantation for AAT-nondeficient patients with COPD and improves survival compared with standard (nontransplant) care.

In a single-center study, the outcomes of 45 patients who underwent lung transplantation for AAT deficiency were compared with those of 231 AAT-nondeficient patients who underwent lung transplantation for COPD.

AAT deficiency was not a risk factor for early or late post-transplant death. Lung transplantation provides both quality of life and survival benefits for selected patients with very severe AATD-related emphysema (29).

In a retrospective case-control study conducted by Tanash HA, et al., 83 patients with advanced emphysema due to AAT deficiency (PI*ZZ) underwent single (62) or bilateral (21) lung transplantation. Survival was compared with 70 nontransplanted AAT deficient individuals of similar age, sex, smoking history and lung function.

The median survival times were significantly longer among transplanted (11 years, 95% CI 9-14) versus nontransplanted (5 years, 95% CI 4-6) patients (30). Lung transplantation was associated with marked improvements in the SGRQ scores across all domains with the total score falling (improving) (3,31).

Banga A, et al. conducted study where 45 patients underwent LT for AAT deficiency - compared with 231 AAT-LT for COPD.

Single lung recipients in both groups experienced a similar rate of decline in FEV1. Among bilateral lung transplant recipients, the rate of decline in FEV1 was greater in those who were AAT deficient compared with those who had normal levels of AAT. The cause of this discrepancy is unclear. No differences in the frequency or severity of acute cellular rejection episodes were observed. The effect of AAT augmentation on lung allograft function could not be assessed, as only six AAT-deficient patients received augmentation after transplantation (29).

Augmentation following lung transplantation

Continuation of AAT augmentation therapy following lung transplantation is controversial, largely because it is costly (1).
Most transplant centers do not give augmentation therapy to AAT deficient lung transplant recipients, as it is not known whether it would improve outcomes or longevity during the patient's lifetime, and significant recurrent emphysema is unlikely to occur for 30 to 40 years in the absence of smoking (29,32).

Observing lung function after transplant augmentation initiation performs only if the patient has persistent lung function decline (28). This practice is supported by a report that two of four lung transplant recipients responded to weekly augmentation therapy after experiencing lung function decline refractory to the usual therapies for bronchiolitis obliterans syndrome (33).

Theoretically, AAT augmentation could also be initiated if characteristic radiologic changes of emphysema were to develop in the absence of lung function decline (28).

Other authors suggest providing once-weekly therapy (60 mg/kg) during conditions associated with an increased neutrophil burden in the lung (as with pneumonia or acute rejection), although data in support of this practice are lacking (29,34,35).

Emerging therapies

A number of emerging therapies that use novel treatment approaches for AATD are being investigated, though none is currently approved for use.

These potential interventions include gene therapy, augmentation therapy using modified proteins that require less frequent infusion, corrector molecules that prevent misfolding and allow more normal secretion of AAT protein that might otherwise polymerize within the hepatocyte, and interfering mRNA that suppresses Z protein expression within the hepatocyte (36).

Further study of these various approaches will clarify whether they have efficacy and will receive regulatory approval for use.

CONCLUSION

All adults with persistent airflow obstruction on spirometry should be tested for AATD. Additional features that should lead clinicians to test for AATD include emphysema in a young and a non-smoker individual, adult-onset asthma as well as a family history of emphysema and/or liver disease.

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The Use of Electroconvulsive Therapy in the Treatment of Schizophrenia

Primjena elektrokonvulzivne terapije u tretmanu shizofrenije

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ABSTRACT

Electroconvulsive therapy (ECT) is an effective and safe treatment for severe mental disorders, including schizophrenia. Although ECT is often the last treatment option after other therapeutic attempts have failed, research shows that it can be particularly effective in patients with resistant forms of schizophrenia.The safety and tolerability of the procedure have been improved through improved technical and medical features over the years. Despite its proven effectiveness, ECT often faces stigma, which can make it difficult to accept its use as a therapeutic option. Therefore, it is important to educate the public about the mentioned therapeutic method, to understand the advantages, but also the potential risks in the context of the modern approach to psychiatric treatment.

Keywords: convulsive therapy, mental disorders, therapeutic effectiveness

SAŽETAK

Elektrokonvulzivna terapija (EKT) je efikasan i siguran tretman za teške psihičke poremećaje, uključujući i shizofreniju. Iako je EKT često posljednja opcija liječenja nakon neuspjeha drugih terapijskih pokušaja, istraživanja pokazuju da može biti posebno djelotvorna kod pacijenata sa rezistentnom formom shizofrenije. Sigurnost i podnošljivost postupka su poboljšane kroz poboljšane tehničke i medicinske karakteristike tokom godina. Unatoč dokazanoj djelotvornosti, EKT se često suočava sa stigmatizacijom, što može otežati prihvatanje primjene kao terapijske opcije. Stoga je važno educirati javnost o navedenoj terapijskoj metodi, razumijeti prednosti, ali i potencijalne rizike u kontekstu modernog pristupa psihijatrijskom liječenju.

Ključne riječi: konvulzivna terapija, mentalni poremećaji, terapijska djelotvornost

INTRODUCTION

Schizophrenia is a disabling condition that affects approximately 1% of the world's population. Symptoms include positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., avolition, anhedonia), and cognitive function impairment (1). Electroconvulsive therapy is an effective and safe procedure, primarily recommended for patients experiencing depressive episodes, bipolar disorder, mania, and schizophrenia when they do not respond to other treatments (2). In such cases, electroconvulsive therapy (ECT) becomes a significant option in treatment. A team of Italian physicians led by Ugo Cerletti (1877–1963) and Lucio Bini (1908-1964) sought to derive a method of electrical seizure induction with a quicker onset and fewer side effects and began by testing their technique in dogs. They inserted one electrode in the mouth and another in the anus, but after observing that this tended to induce cardiac arrest, they refined their procedure to focus the electrical current cranially. In 1938, they conducted their first human trial on a 39-year-old disorganized man with schizophrenia. With the application of 110 volts of alternating current for 0.2 seconds, they successfully induced a seizure (3). They administered ten more treatments over the course of the patient's hospitalization and successfully attenuated his psychosis, such that he was able to return to his wife and job in the community.

In the 1980s, significant changes were made that reintroduced this therapy into psychiatric institutions. The changes improved ECT, making it safer. The number of indications was reduced to only two main ones, which are catatonic schizophrenia and treatment-resistant depression. Today, ECT is used in targeted indications, with technical, legal, and medical procedures that enable supervision, better effectiveness, and greater safety (4).

AIM

The aim of the paper was to present new knowledge about the electroconvulsive therapy in the treatment of schizophrenia.

Procedure of ECT Execution

The environment in which ECT is performed must be safe, and patients waiting should not hear or see the procedure currently being performed. A thorough medical history must be taken. If a unilateral model is used, electrodes are placed on the non-dominant hemisphere. If the patient is right-handed, their dominant hemisphere is typically the left. However, if the patient is left-handed, both hemispheres may be dominant, so a bilateral model is then recommended. The anesthesia procedure is standard. The patient should not eat or drink for at least five hours before the procedure. The anesthesiologist checks the patient's dental status. In addition to the psychiatrist and anesthesiologist, at least one nurse should be present. The anesthesiologist is responsible for selecting medications and maintaining vital functions during anesthesia. While the anesthesiologist induces anesthesia, the psychiatrist checks the electrode placement and the dose of electrical energy. The skin should be cleaned, after which moistened electrodes are applied to the patient's scalp.

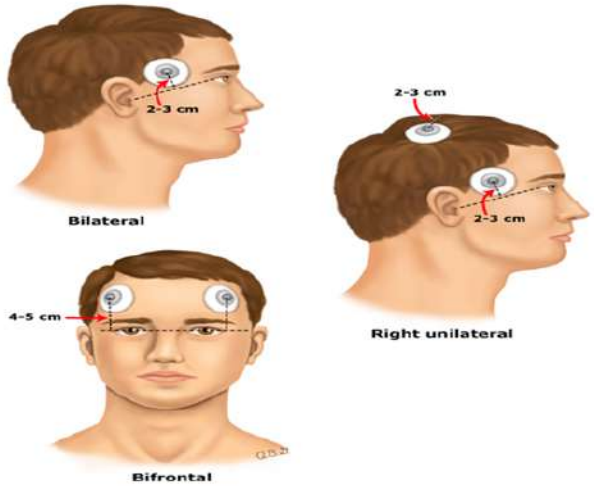

Figure 1 **Placement of electrodes for ECT.**

In the case of unilateral ECT, the first electrode is placed on the non-dominant side, 3 cm above the midpoint between the outer edge of the orbit and the external auditory canal. The second electrode is placed at least 10 cm away, vertically above the auditory canal on the same side. After electrode placement, a stimulus in the form of an appropriate dose of electrical energy is administered. It is recommended to use the electrical energy dose that induces seizures lasting between 20 to 50 seconds. Anesthesia can be safely administered even in patients on therapy. After the procedure, the patient remains under the supervision of the anesthesiologist until autonomous breathing and consciousness are reestablished. The psychiatrist should write a brief report on the procedure, the doses of electrical energy used, and any potential complications. ECT is typically performed twice a week, and the duration of treatment depends on clinical assessment, averaging from 6 to a maximum of 12 sessions (4).

Side Effects of ECT

The administration of ECT may be accompanied by headaches and anxiety, brief disorientation (especially in bilateral ECT), short-term retrograde amnesia, as well as anterograde memory loss lasting for 30 minutes after the procedure. Some patients may also complain of confusion, nausea, and dizziness for several hours after the procedure. Muscle aches may also be reported by some patients. There is a possibility of damage to the teeth, tongue, or lips if airway or other aids are inadequately positioned. Other reported side effects include vertebral fractures, only if ECT is performed without muscle relaxants, which should never be the practice today (4).

MATERIALS AND METHODS

In this study, we employed a systematic approach to gather and analyze relevant data regarding the application of electroconvulsive therapy (ECT) in the treatment of schizophrenia. The research was conducted by searching multiple databases and scientific sources to ensure a broad spectrum of information and research papers. Specifically, searches were conducted in the following databases:

1. PubMed
2. Google Scholar
3. Article searches - additional searches of relevant articles published in scientific journals and publications
4. Available literature - (relevant textbooks on psychiatry). The search encompassed randomized studies published in the last five

years, with the aim of collecting the most recent data and research. Keywords used during the searches included terms such as "electroconvulsive therapy," "ECT," "schizophrenia," "treatment-resistant schizophrenia," "efficacy of ECT," and similar. All selected studies were thoroughly reviewed and analyzed to identify the most important information regarding the effectiveness, safety, mechanisms of action, and benefits and risks of applying ECT in the treatment of schizophrenia. This methodological approach enabled the collection of comprehensive data, ensuring the relevance and reliability of the conclusions of this study.

DISCUSSION

The results of the analysis of relevant literature and clinical studies on the application of electroconvulsive therapy (ECT) in the treatment of schizophrenia indicate several key findings worthy of detailed discussion.

Effectiveness of ECT in treating schizophrenia

Research consistently shows that ECT can be particularly effective in cases of schizophrenia resistant to pharmacotherapy. In the reviewed and analyzed studies, the objectives were as follows: evaluation of the efficacy of clozapine in patients with treatment-resistant schizophrenia (TRS) and the efficacy of ECT augmentation of clozapine in patients with ultra-treatment-resistant schizophrenia (UTRS), where both approaches resulted in improvement in CGI scores. Both Clozapine and ECT are effective therapeutic options for patients with TRS and UTRS (5). In the next study, the aim was to determine the efficacy of ECT in patients with schizophrenia who do not show resistance to Clozapine and compare it with a group of patients with Clozapine-resistant schizophrenia. The study was conducted on 68 patients, concluding that ECT is an effective augmentation strategy for patients with CRS and is equally effective as when used in patients without CRS (6). In a retrospective study involving 309 patients, it was concluded that the use of ECT may be most beneficial in patients receiving Clozapine (7).

Safety and Tolerability of ECT

Changes that improved ECT in the 1980s made it safer and more effective. First, the number of indications was reduced to only two main ones, which are catatonic schizophrenia and treatment-resistant depression. Second, the patient voluntarily consents to ECT. Third, before administering ECT, medical evaluation is performed to exclude physical illnesses in which this therapy could be harmful (high blood pressure, heart diseases, implanted pacemaker, etc.). Fourth, technical features of the ECT apparatus have been changed. Thus, the current strength varies according to the indication, number of applications, etc. It involves alternating current with a strength ranging from 100 to 600 mA and a voltage from 70 to 130V. Fifth, ECT is administered under general anesthesia, and the patient receives a muscle relaxant (3). The results of clinical studies indicate that acute electroconvulsive therapy resulted in improvement of psychotic symptoms in almost all elderly patients, many of whom had treatment-resistant conditions. No deaths or serious medical complications associated with electroconvulsive therapy were recorded (8). Another study suggests that ECT is a highly effective and safe treatment in older adults with schizophrenia who have inadequately responded to psychotropic medications. The study included 20 patients with an average age of 69 years. Patients had undergone an average of seven different antipsychotic medications before acute ECT treatment; 50% had been treated with clozapine. ECT was associated with complete (60%) or partial (35%) improvement in psychotic illness in 95% (n = 19) of patients. There were no deaths (9). Recent findings indicate that the use of ECT in the pediatric population is limited to severe and refractory psychiatric conditions, including depression, bipolar disorder, schizophrenia, suicidal and self-injurious behavior, neuroleptic malignant syndrome, and catatonia, with common side effects including memory disturbances, headache, confusion, and nausea, which are usually transient and self-resolving (10). Studies suggest that ECT in schizophrenia is a safe therapeutic method, but the potential for cognitive difficulties should always be carefully assessed (11).

Mechanisms of Action

There is a need to understand the basic physiological, cellular, and molecular mechanisms of ECT in order to devise strategies for optimizing therapeutic outcomes (12). Electroconvulsive therapy (ECT) has been successfully used for almost a century, but its mechanisms of action remain poorly understood (13). To date, many theories about the mechanism of action have been proposed, classified into neurophysiological, neurobiochemical, and neuroplastic processes. Proposed mechanisms have included neurotransmitters, neurotrophic factors, the immune system, the hypothalamic-pituitary-adrenal axis, neuroplasticity, epigenetic modifications, brain neurophysiology, cerebral circulation, and brain structure (14). The mechanisms of action of ECT involve modifications of neurobiological functions and changes in the immune and endocrine systems that occur after ECT. Among them are described reductions in hyperconnectivity of neural networks, reductions in neuroinflammation, promotion of neurogenesis, modulation of various monoaminergic systems, and normalization of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes (15).

Stigmatization in the Application of ECT

ECT is often used as a last resort treatment, after other thera pies have failed to produce satisfactory results. ECT is frequently portrayed inaccurately and negatively in popular media, resulting in controversial public opinion and increased stigmatization (4). ECT is underutilized largely due to persisting stigma and lack of knowledge about modern ECT technique. Due to potential side effects and stigma associated with the procedure, ECT is typically not used as a first-line treatment method.

CONCLUSION

Electroconvulsive therapy (ECT) remains a valuable and effective treatment option for severe psychiatric conditions such as schizophrenia, especially in cases resistant to other forms of therapy. Despite historical misconceptions and stigma, contemporary research highlights the safety and efficacy of ECT when properly administered. Advances in technique and patient selection have contributed to improved tolerability and reduced risk of side effects. Furthermore, further efforts are needed to educate both healthcare professionals and the public about the benefits of ECT and to debunk misconceptions and prejudices associated with this treatment method. By fostering greater understanding and acceptance, ECT can continue to play a crucial role in comprehensive care for individuals with severe mental illnesses.

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Case Report of Retroperitoneal Liposarcoma: Diagnosis, Surgical Treatment, and Rehabilitation

Prikaz slučaja: retroperitonealni liposarkom, dijagnostika, kirurški tretman I liječenje

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ABSTRACT

Introduction: retroperitoneal liposarcoma is a rare and aggressive soft tissue tumor, typically presenting with nonspecific symptoms. This case report describes a 68-year-old female patient diagnosed with a large retroperitoneal mass, initially presenting with mild and intermittent nausea. The diagnosis was confirmed through a series of diagnostic imaging, including contrast-enhanced CT of the abdomen and pelvis, which revealed a heterogeneous mass with lipomatous and necrotic components, suggestive of liposarcoma. The mass exerted considerable pressure on adjacent structures, including the right kidney, colon, and duodenum. A multidisciplinary oncology team decided on surgical intervention. The patient underwent an extensive surgical resection, including right nephrectomy, right hemicolectomy, and resection of the retroperitoneal mass. The procedure was successful, and the patient experienced a relatively smooth postoperative recovery. Postoperative monitoring and follow-up imaging showed no immediate complications. The histopathological examination of the resected tissue confirmed the diagnosis of retroperitoneal liposarcoma. This case highlights the importance of early detection through advanced imaging techniques and the critical role of surgical resection in the management of retroperitoneal liposarcoma. Given the tumor's tendency for recurrence, long-term follow-up and surveillance are crucial to ensure the patient's continued health. Conclusion: this report emphasizes the need for a multidisciplinary approach, involving oncologists, surgeons, and radiologists, to achieve the best outcomes in the treatment of rare soft tissue sarcomas.

Keywords: liposarcoma, retroperitoneal tumor, surgical resection, CT imaging, nephrectomy, soft tissue sarcoma, postoperative care, oncology treatment

SAŽETAK

Uvod: retroperitonealni liposarkom je rijedak i agresivan tumor mekog tkiva, koji obično pokazuje nespecifične simptome. Ovaj prikaz slučaja opisuje pacijenticu u dobi od 68 godina kojoj je dijagnosticirana velika tumorska masa u retroperitoneumu, koja je inicijalno imala blage i povremene mučnine. Dijagnoza je potvrđena kroz niz dijagnostičkih postupaka, uključujući kontrastni CT abdomena i zdjelice, koji su prikazali heterogenu masu sa lipomatoznim i nekrotičnim komponentama, što je sugerirao liposarkom. Masa je vršila veliki pritisak na susjedne strukture, uključujući desni bubreg, debelo crijevo i duodenum. Multidisciplinarni onkološki tim odlučio je na kiruršku intervenciju. Pacijentica je podvrgnuta opsežnoj kirurškoj resekciji, uključujući desnu nefrektomiju, desnu hemikolektomiju i resekciju retroperitonealne mase. Procedura je bila uspješna, a pacijentica je imala relativno glatki postoperativni oporavak. Postoperativno praćenje i kontrolni pregledi pokazali su da nije bilo neposrednih komplikacija. Histopatološki nalaz odstranjenog tkiva potvrdio je dijagnozu retroperitonealnog liposarkoma. Ovaj slučaj ističe važnost rane detekcije uz pomoć naprednih dijagnostičkih tehnika i ključnu ulogu kirurške resekcije u liječenju retroperitonealnog liposarkoma. S obzirom na tendenciju tumora ka recidivu, dugoročno praćenje i nadzor su od esencijalne važnosti za održavanje zdravlja pacijentice. Zaključak: ovaj izvještaj naglašava potrebu za multidisciplinarnim pristupom, koji uključuje onkologe, kirurge i radiologe, kako bi se postigao najbolji ishod u liječenju rijetkih sarkoma mekog tkiva.

Ključne riječi: liposarkom, retroperitonealni tumor, kirurška resekcija, CT snimanje, nefrektomija, sarkom mekog tkiva, postoperativna njega, onkološko liječenje

INTRODUCTION

Liposarcoma is a rare malignant tumor originating from adipose tissue and is classified as a soft tissue sarcoma. Although it most commonly occurs in the lower extremities and retroperitoneum, it can also develop in other parts of the body (1).

Retroperitoneal liposarcoma is particularly challenging due to its location, which complicates early diagnosis and effective treatment. The retroperitoneum is a space located behind the peritoneum, encompassing vital organs such as the kidneys, adrenal glands, major blood vessels, and part of the digestive system (2).

Therefore, the clinical presentation of retroperitoneal liposarco ma is often nonspecific, and symptoms can be mistaken for diseases of other organ systems, leading to a delay in diagnosis. Symptoms of liposarcoma may include abdominal pain, shortness of breath, digestive disturbances, weight loss, and general weakness (3).

However, patients with retroperitoneal liposarcomas often remain asymptomatic until the tumor reaches a significant size and compresses surrounding organs. This delay in diagnosis can significantly impact the prognosis of the disease, as the cancer may spread or become inoperable. The diagnosis is typically made through a combination of clinical examination, radiological imaging (commonly CT or MRI), and histopathological analysis (4).

In this case, we will present the clinical course of a 68-year-old female patient who, after experiencing a range of nonspecific symptoms, was diagnosed with retroperitoneal liposarcoma. We will provide a detailed description of the diagnostic procedures, therapeutic interventions, and the postoperative course of the patient, analyzing the challenges in treatment and the outcomes of the surgical procedure.

CASE REPORT

A 68-year-old female patient was admitted to the Department of General and Abdominal Surgery of the CCUS for surgical treatment of a retroperitoneal tumor. The patient reported no major symptoms, except for occasional nausea. However, due to a decrease in her hemogram, additional diagnostic procedures were performed, including an abdominal CT scan, which revealed a large mass in the retroperitoneum.

The abdominal CT, performed on 31 September 2024, identified a mass primarily located in the right side of the abdomen, ventral to the right kidney, measuring 107x29x98 mm. The mass was heterogeneous, with a hypodense central region indicative of central necrosis. The mass caused significant compression of adjacent organs, including the right kidney, duodenum, and pancreas, although there appeared to be no direct connection with the kidney. A large lipomatous component with a fibrous network surrounded the tumor, filling a significant portion of the abdomen and mesenteric space. This finding raised suspicion of a malignant liposarcoma, as the lipomatous component along with the necrotic areas in the center suggested this diagnosis.

Additionally, a contrast-enhanced CT angiography (CTA) of the abdomen and pelvis was performed on 26 September 2024, which provided detailed imaging of the expansive tumor mass in the right side of the abdomen. The CTA clearly showed that the mass was predominantly composed of macroscopic fat but also contained solid components that enhanced peripherally with contrast, while the central area was hypodense. The tumor mass was in close proximity to the right kidney and right renal artery, causing compression of the right kidney and ureter. These radiological findings, including evidence of tissue infiltration, were crucial in raising suspicion of liposarcoma. The CTA also indicated the absence of enlarged lymph nodes, which was positive in terms of ruling out lymphogenic spread of the disease.

Laboratory results also contributed to assessing the patient's condition. Hematological findings indicated leukocytosis (16.10 x10^9/L), low erythrocyte (3.44 x10^12/L), hemoglobin (100 g/L), and hematocrit (31%) levels, suggesting anemia and an inflammatory response. Additionally, elevated CRP (67.7 mg/L) could indicate inflammation associated with a malignant process. Other parameters, such as a high platelet count (560 x10^9/L), also pointed to a systemic reaction to the tumor.

Based on these findings, particularly the radiological criteria from the CT and CTA scans, suspicion of retroperitoneal liposarcoma was raised. A percutaneous needle biopsy was recommended to confirm the diagnosis.

Therapeutic Approach

After the diagnosis of retroperitoneal liposarcoma was confirmed through radiological and laboratory findings, it was decided that the patient would undergo surgical intervention. The surgery was scheduled for 7 October 2024. Prior to the procedure, the patient underwent preoperative assessments, including laboratory tests, cardiac monitoring, and abdominal preparation for surgery.

The operation began with a median laparotomy incision, which provided excellent access to the retroperitoneal mass. During the initial exploration of the surgical site, the surgeons identified a large tumor mass located in the retroperitoneal space. The mass predominantly occupied the right hemiabdomen and was in close proximity to the right kidney, right ureter, right colon, and mesocolon. The tumor was compressing and infiltrating the adjacent organs, including the cecum, ascending colon, and duodenum. The right kidney and ureter were embedded within the tumor mass itself, presenting a significant challenge for the surgical team.

Given the extent of the infiltration into the right kidney, it was decided to perform a right nephrectomy alongside the tumor resection. The tumor mass, right kidney, right colon, and mesocolon were completely excised. During the operation, the duodenum had to be carefully mobilized at several points, and the pancreas was in close contact with the mass, which further complicated the procedure. At these stages, the duodenum was carefully separated from the tumor, and sutures were used to properly detach and protect these structures (Figure 1,2).

After the tumor was excised, an ileotransversostomy was performed to connect the ileum with the transverse colon. The anastomosis was completed in two layers using PDS 3-0 sutures to ensure proper intestinal continuity and prevent leakage. At the end of the procedure, hemostasis was successfully achieved, and a drain was placed to allow for the removal of secretions from the surgical site (Figure 3,4,5).

Postoperatively, the patient was transferred to the intensive care unit for close monitoring of vital signs and further resuscitation. The day after the surgery, the patient was stable, with vital parameters within normal ranges. Bowel movements were spontaneously reestablished, which was a positive indicator of functional recovery.

On the third postoperative day, the patient was transferred to the regular ward with stable vital signs. Although the postoperative recovery was uneventful, continuous monitoring and control of laboratory parameters, including hemoglobin, white blood cells, and CRP, were necessary to detect any potential postoperative complications or infections in a timely manner.

During the postoperative period, rehabilitation measures were also implemented, including physiotherapy and controlled physical activities, to expedite recovery and prevent other complications. Additionally, regular follow-up visits and radiological exams were scheduled to monitor the status of the excised tumor and exclude the possibility of recurrence or metastasis.

Thanks to the successful surgery and postoperative care, the patient was discharged from the hospital in stable condition after a few days. Further follow-up will include oncological surveillance and preventive measures to avoid disease recurrence.

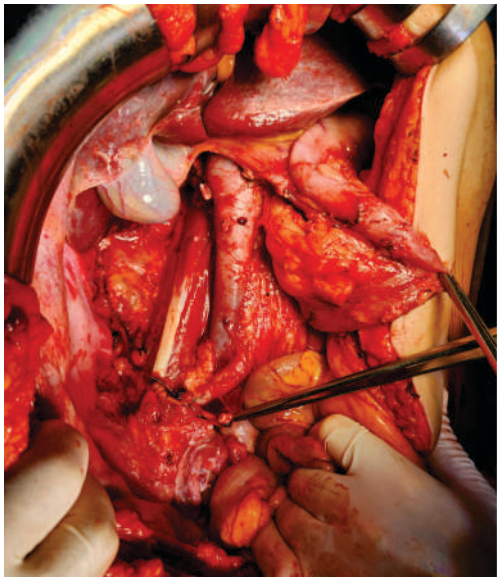

Figure 1 **Vascular stalk view**

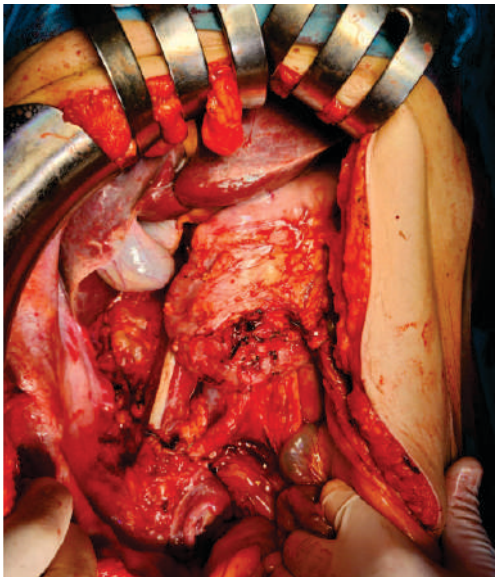

Figure 2 **Tumor lodge view.**

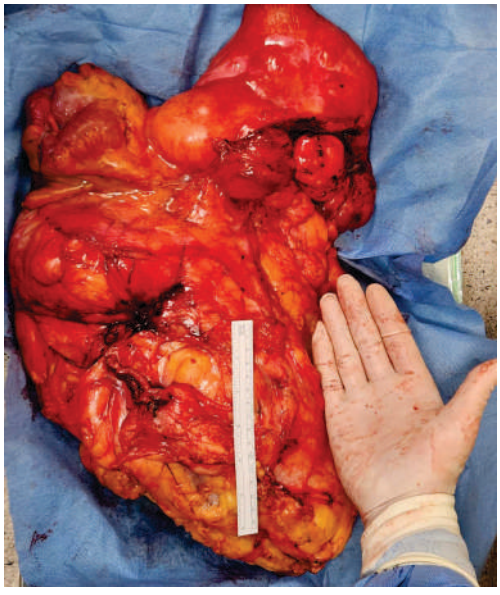

Figure 3 **Size of tumor comparing to man's hand.**

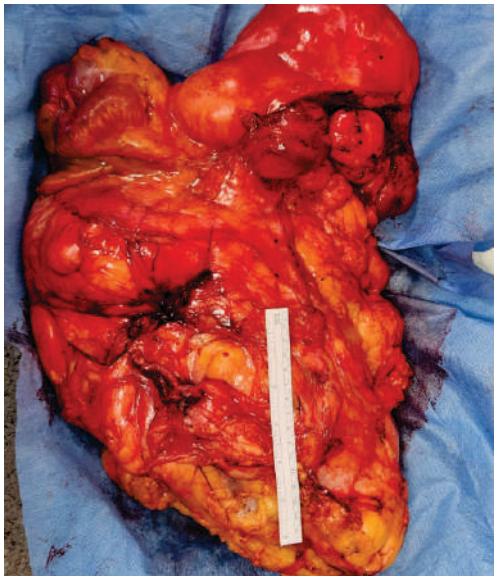

Figure 4 **Size of tumor with centimeter marker.**

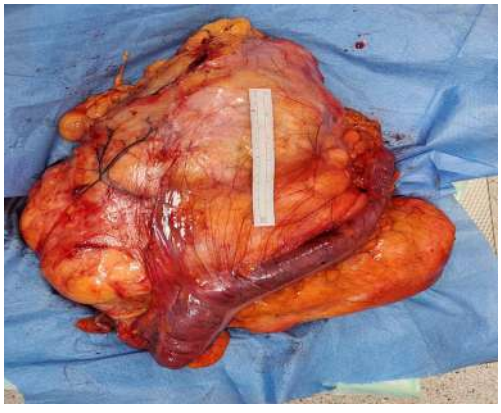

Figure 5 **Completely excised tumor.**

DISCUSSION

Retroperitoneal liposarcoma is a rare but serious form of soft tissue tumor, often remaining undiagnosed in its early stages due to its asymptomatic nature. In this case report, the patient exhibited minimal symptoms, including occasional nausea, which may have delayed the diagnosis. One of the key diagnostic challenges of retroperitoneal liposarcomas is their nonspecific symptoms and the difficulty in recognizing them at an early stage, requiring thorough radiological investigation (5).

CT of the abdomen and pelvis was crucial in diagnosing liposarcoma. Detailed radiological findings indicated a mass predominantly in the right retroperitoneal space, with lipomatous components and areas of necrosis, a characteristic indication of liposarcoma. CT angiography also provided additional information on the tumor's vascularization, aiding in precise surgical planning. Given the tumor's size and its infiltration into adjacent organs, an aggressive surgical approach was chosen, including complete resection of the tumor, the right kidney, and part of the colon. This approach was necessary to prevent further disease progression and ensure control over the tumor's spread (6).

The surgery required a high level of skill and coordination from the team, which included specialists in abdominal surgery and urology. Although there were technical difficulties in separating the duodenum and pancreas from the tumor, the surgery was successfully completed. The patient showed good postoperative recovery, with normalization of vital parameters and successful continuation of therapy. However, as is often the case with liposarcomas, there is a risk of recurrence, which requires regular monitoring and oncological follow-up in the coming months and years.

Retroperitoneal liposarcoma, although rare, necessitates timely diagnosis and proper therapeutic management. In this case, early tumor detection through CT imaging, combined with surgical resection, allowed the patient to recover and avoid further complications. However, given that liposarcomas have a high potential for recurrence, the patient will undergo regular check-ups, including radiological exams and laboratory tests. Long-term follow-up is crucial for early detection of recurrence or metastasis, as well as for determining the need for adjuvant therapy if needed (7).

CONCLUSION

The surgical procedure in this case was successful and allowed the patient to improve their quality of life. Despite the early successful intervention, it is crucial for the patient to remain under constant supervision to minimize the risk of recurrence, which is common with liposarcomas. Therefore, a multidisciplinary approach, including surgical, oncological, and radiological monitoring, is essential for optimal management of this serious condition.

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Psychiatric Dilemma: Are Symptoms a Consequence of Illness or Substance Use?

Psihijatrijska dilema: Da li su simptomi posljedica bolesti ili upotrebe psihoaktivnih supstanci?

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ABSTRACT

Introduction: the concurrence of two or more psychiatric disorders in the same individual (comorbidity or dual diagnosis) is not a rare exception. The term "dual diagnosis" dates back to the 1980s, with frequent identification beginning in the 1990s. Recent meta-analyses have shown that the prevalence of dual diagnoses exceeds 50%, and the comorbidity rate of substance use disorders among patients with schizophrenia is almost three times higher than in the general population. Both conditions are characterized by alterations in mental functions, personality deterioration, and a decline in overall functionality. This phenomenon complicates both diagnosis and treatment outcomes, increasing the number of hospitalizations, relapses, and suicide attempts. Case report: we present the case of a 42-year-old patient with a positive psychiatric family history. Through multiple hospitalizations, the patient displayed a wide range of psychotic symptoms within a complex and fluctuating clinical picture, accompanied by a decline in overall functionality. The triggering factor was the use of psychoactive substances starting in early adolescence. Consequently, the clinical presentation was often attributed to substance abuse. However, due to repeated hospitalizations and negative screening tests for psychoactive substances, it became evident that the dominant symptomatology resulted from the underlying illness rather than substance abuse. In this case, substance use accelerated the disease's progression and functional decline. Considering the primary diagnosis, the patient's difficult socioeconomic situation, frequent hospitalizations, and the poor prognosis of the illness, the patient was placed in the Institution for the Care of Mentally Disabled Persons - Drin, where he currently resides. With a recommended daily dose of 150 mg clozapine and 50 mg sertraline, the patient functions in accordance with his capacities and disease progression. Conclusion: recognizing the connection between the psychiatric diagnostic entity of schizophrenia (SCH) and substance use disorders (SUD) is one of the main focuses of current psychiatric research. It has implications for evaluating the diagnostic boundaries of both conditions and for developing improved psychopharmacological treatments.

Keywords: comorbidity, schizophrenia, substance use disorders, psychopharmacological treatment

SAŽETAK

Uvod: podudarnost dva ili više psihijatrijskih poremećaja kod ste osobe (komorbiditet ili dualna dijagnoza) nije rijetka iznimka. Pojam „dualne dijagnoze" datira iz 1980-ih godina, a njihova česta identifikacija počinje 1990-ih godina. Nedavne meta-analize su pokazala da je prevalenca dualnih dijagnoza veća od 50 %, a da je skoro tri puta veća stopa komorbiditeta poremećaja upotrebe psihoaktivnih supstanci kod pacijenata sa shizofrenijom nego u općoj populaciji. Oba poremećaja su karakterizirana izmjenama psihičkih funkcija i deterioracijom ličnosti, te pada opće funkcionalnosti. Ova pojava kompliciira kako postavljanje dijagnoze, tako i ishode liječenja psihijatrijskih pacijenata te povećava broj hospitalizacija, remisija i pokušaja suicida. Prikaz slučaja: prezentujemo slučaj 42-godišnjeg pacijenta koji ima pozitivan psihijatrijski hereditet. Kroz veći broj hospitalizacija pacijent ispoljava širok spektar simptoma psihotičnog karaktera u kompleksnoj i fluktuirajućoj kliničkoj slici uz pad opšte funkcionalnosti. Deklanširajući faktor je bio upotreba psihoaktivnih supstanci od ranog adolescentnog perioda, te se prezentovana klinička slika često smatrala posljedicom zloupotrebe istih. Obzirom na opetovane hospitalizacije i negativne screening testove na psihoaktivne supstance, postaje jasno da je dominantna simptomatologija posljedica osnovne bolesti, a ne zloupotrebe psihoaktivnih supstanci, koji su u ovom slučaju doveli do brže progresije bolesti i pada opšte funkcionalnosti. Imajući u vidu osnovnu dijagnozu, uz tešku socioekonomsku situaciju pacijenta, česte hospitalizacije kao i nepovoljan prognostički tok same bolesti, pacijent se smješta u Zavod za zbrinjavanje mentalno invalidnih osoba- Drin gdje se i sada nalazi. Uz preporučenu terapiju klozapin u dnevnoj dozi od 150 mg i sertralin u dozi od 50 mg funkcioniše u skladu sa svojim kapacitetima i progresijom osnovne bolesti. Zaključak: prepoznavanje veze između psihijatrijskog dijagnostičkog entiteta shizofrenije (SCH) i ovisnosti o psihoaktivnim supstancama (PAS) jedan je od glavnih fokusa novijih psihijatrijskih istraživanja, sa implikacijama za evaluaciju dijagnostičkih granica oba poremećaja i razvoj boljeg psihofarmakoterapijskog tretmana.

Ključne riječi: komorbiditet, shizofrenija, ovisnost o psihoaktivnim supstancama, psihofarmakološki tretman

INTRODUCTION

The concurrence of two or more psychiatric disorders in the same individual (comorbidity or dual diagnosis) is not a rare exception. The term 'dual diagnosis' dates back to the 1980s, with frequent identification beginning in the 1990s. Since then, various definitions have emerged, but a universally accepted and unambiguous definition remains elusive. Currently, the World Health Organization (WHO) defines dual diagnosis as 'the simultaneous occurrence of a psychoactive substance use disorder and another psychiatric disorder in the same person,' reflecting the complexity and overlapping nature of these conditions. This phenomenon complicates both diagnosis and treatment outcomes, increasing the number of hospitalizations, remissions, and suicide attempts.

Recent meta-analyses have shown that the prevalence of dual diagnoses exceeds 50%, and that the rate of substance use disorder comorbidity among patients with schizophrenia is nearly three times higher than in the general population. It has also been shown that men with schizophrenia are more vulnerable to developing substance use disorders.

There are several hypotheses regarding the frequent occur rence of dual diagnoses in individuals with psychiatric disorders. The 'self-medication' hypothesis suggests that individuals attempt to treat symptoms of their mental illness with alcohol or psychoactive substances, while the biological sensitivity hypothesis proposes that individuals with psychiatric disorders are more sensitive to lower doses of substances, leading to a higher risk of addiction. Many researchers have also proposed a neurobiological hypothesis to explain this comorbidity - the mesocorticolimbic reward circuit in the brain may be the underlying mechanism of comorbidity of substance use disorders in patients with schizophrenia. Key neurotransmitters involved may include opioids, catecholamines (especially dopamine), and gamma-aminobutyric acid (GABA). Dopaminergic neurons in the ventral tegmental area are especially important. These neurons project into the cortical and limbic regions, particularly the nucleus accumbens. This pathway is likely involved in the brain's reward system and may mediate the effects of psychoactive substances.

Schizophrenia is a complex mental disorder characterized by positive symptoms (hallucinations, delusions, formal thought disorder) and negative symptoms (apathy, poverty of speech, emotional blunting). Substance abuse can also lead to these symptoms, depending on the substance used, which often causes overlap and masks the individual's true condition. People with schizophrenia often avoid social interactions due to paranoia, hallucinations, or disinterest in their environment, while those using heroin may isolate due to addiction, stigmatization, or lifestyle changes. Disorganized thinking, attention and memory problems are present in schizophrenia, while prolonged heroin use can cause concentration, memory, and decision-making problems. Emotional blunting in schizophrenia includes diminished emotional responses, monotonous speech, and apathy; heroin's sedative effects may cause similar symptoms. Schizophrenia can lead to avolition, while heroin users often neglect responsibilities, jobs, and hygiene. Although heroin itself does not induce psychosis, long-term addiction, withdrawal, or mixing substances can result in paranoid thoughts and perceptual disturbances. Since schizophrenia typically includes hallucinations and delusions, understanding the relationship between these two psychiatric entities is a major focus of current research, with implications for evaluating diagnostic boundaries and improving psychopharmacological treatment.

Studies show that atypical antipsychotics such as clozapine, risperidone, and olanzapine are effective in controlling psychotic symptoms and reducing substance use in individuals with dual diagnosis. Specifically, recent studies indicate that clozapine treatment is significantly associated with sustained abstinence from psychoactive substances and reduced likelihood of psychiatric hospitalization compared to other antipsychotic treatments.

CASE REPORT

A 42-year-old man living with a roommate, was admitted to the Clinic of Psychiatry of the Clinical Center University of Sarajevo as a transfer from the Angiology Clinic, where he was treated for Phlebotrombosis iliacofemoropoplitealis I. sin., due to changes in mental status and behavior, manifested as paranoid interpretations of reality and perceptual disturbances. The patient had been undergoing psychiatric treatment for the past five years and reported the use of olanzapine, haloperidol, sertraline, nitrazepam, among others. He also stated that he had undergone treatment several times at the Institute for Addiction Disorders of Canton Sarajevo and that he was currently on methadone substitution therapy. Previously, he had been treated with buprenorphine+naltrexone following many years of heroin use. Upon admission, he did not possess any supporting medical documentation.

The patient reported a positive family history of psychiatric illness; his father died by suicide, jumping from a building -"he was mentally ill, but refused treatment." His mother passed away five years ago, which coincided with his first psychiatric hospitalization and encounter with a psychiatrist. He has a half-sister from his father's first marriage whom he describes as very withdrawn, with whom he has no close relationship - "I think she is depressed."

During hospitalization at the Clinic of Psychiatry, the patient displayed symptoms of withdrawal, prompting a consultation with an addiction specialist from the Institute for Addiction Disorders. The patient's treatment history at the mentioned institution was confirmed and supported with medical records. A review of these records revealed that the patient began experimenting with psychoactive substances during high school—initially marijuana, later progressing to heroin, which he used nasally for many years. Since 2009, he had intermittently been on substitution therapy (methadone, buprenorphine+naltrexone) but discontinued treatment due to irregular attendance. During this period, he also visited a psychiatrist at the local Mental Health Center due to "low mood" and was prescribed sertraline, which had limited effect due to irregular use.

His first psychiatric hospitalization occurred in 2018, coinciding with his mother's death, when he experienced his first psychotic episode. During the hospitalization at the Psychiatric Hospital of Canton Sarajevo, haloperidol was prescribed. However, after discharge, he resumed heroin use and discontinued pharmacotherapy. He was discharged with the diagnosis of "Mental and behavioral disorders due to use of multiple substances and other psychoactive drugs - abuse." In the post-hospital period, he committed several criminal offenses, which preceded his admission to the Angiology Clinic at CCUS, following a gunshot wound to the leg during a traffic-related firearm incident. After treatment of the injuries, he was transferred to the Psychiatry Clinic at CCUS, where the authors first encountered him.

During hospitalization, the patient was included in a methadone substitution program at an initial dose of 5 mg, but due to administrative reasons, it was administered only once. He was treated only with haloperidol and diazepam injections. A general decline in functioning was observed, and delusions of reference and persecution persisted. After a few days of pharmacotherapy, his emotional investment in these delusions decreased. However, due to the emergence of extrapyramidal symptoms - stiffness of the limbs - haloperidol was discontinued, and biperiden was administered for several days. Clozapine was introduced, gradually titrated to a daily dose of 200 mg. Laboratory values, including leukocytes and neutrophils, remained within reference ranges. The patient responded well to the newly introduced therapy, psychotic symptoms were reduced, and he was discharged with diagnoses of Paranoid Schizophrenia and Mental and behavioral disorders due to use of multiple substances and other psychoactive drugs - dependence syndrome, with a recommendation for follow-up care at the Institute for Addiction Disorders of Canton Sarajevo.

A month later, the patient was rehospitalized at the CCUS Psychiatry Clinic due to symptom exacerbation caused by discontinuation of pharmacotherapy. He denied substance use, and a urine drug screening confirmed this by returning completely negative. During this hospitalization, clozapine was again gradually titrated to a daily dose of 150 mg, and the antidepressant sertraline was introduced at a daily dose of 50 mg. With this treatment, the patient showed certain improvements - better mood and remission of psychotic symptoms-and was discharged in an initial state of remission.

Within one year, the patient was hospitalized at the CCUS Psychiatry Clinic five times, with increasingly shorter intervals between hospitalizations. Each admission followed discontinuation of prescribed pharmacotherapy, with a dominant psychotic symptom profile and declining general functionality. Notably, during this period, the patient did not use psychoactive substances, which was confirmed by consistently negative screening tests. After repeated hospitalizations and negative drug screenings, a definitive diagnosis of Paranoid Schizophrenia was established. Given the primary diagnosis, the patient's difficult socioeconomic situation, frequent hospitalizations, and poor prognosis of the illness, he was placed in the Institution for the Care of Mentally Disabled Persons - Drin, through the efforts of the clinic's social worker and the relevant social services. He currently resides there. With prescribed clozapine at a daily dose of 150 mg and sertraline at 50 mg, he functions within the limits of his capacity and the progression of the illness.

CONCLUSION

The intricate interplay between symptoms of schizophrenia and substance abuse presents a difficulty in adequate psychiatric diagnosis and treatment. Recognizing the connection between the psychiatric diagnostic entity of schizophrenia and substance use disorders is one of the main focuses of current psychiatric research which is necessary in order to provide an adequate psychopharmacological treatment to the patient.

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A Rare Case of Extramammary Myofibroblastoma Arising in the Thoracic Wall and Axilla

Prikaz rijetkog slučaja ekstramamarne prezentacije miofibroblastoma lokalizacije prednjeg torakalnog zida i pazušne jame

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ABSTRACT

Introduction: myofibroblastoma is a rare benign mesenchymal tumor most commonly found in the breast but may also arise in extramammary soft tissue sites. Mammary-type myofibroblastomas outside the breast are uncommon and can mimic malignant neoplasms, particularly when occurring in atypical locations such as the thoracic wall or axilla. Case report: we report the case of a 58-year-old patient who presented with a rapidly enlarging mass in the left lateral thoracic wall and axillary region, accompanied by shoulder movement restriction and upper extremity swelling. Imaging revealed a well-circumscribed, non-invasive soft tissue tumor measuring approximately 19×13 cm. Core biopsy suggested a mesenchymal tumor, and surgical excision was performed. Histopathological and immunohistochemical analysis confirmed the diagnosis of myofibroblastoma. The patient recovered uneventfully postoperatively and remains disease-free at one-year follow-up. Conclusion: this case highlights the importance of including myofibroblastoma in the differential diagnosis of large, benign-appearing soft tissue masses in atypical locations. Awareness of its clinicopathologic features is essential to avoid misdiagnosis and overtreatment. Complete excision is curative, and prognosis is excellent.

Keywords: myofibroblastoma, benign spindle cell tumor, soft tissue neoplasm, thoracic wall mass

SAŽETAK

Uvod: miofibroblastom je rijedak benigni mezenhimalni tumor koji se najčešće javlja u dojci, ali se može pojaviti i na ekstramamarijalnim lokalizacijama u mekim tkivima. Ekstramamarijalni miofibroblastomi tipa dojke su neuobičajeni i mogu imitirati maligne neoplazme, posebno kada se nalaze na atipičnim mjestima poput torakalnog zida ili aksile. Prikaz slučaja: prikazujemo slučaj 58-godišnje pacijentice koja se javila sa brzo rastućom masom u lijevom lateralnom torakalnom zidu i aksilarnoj regiji, praćenom ograničenjem pokreta ramena i otokom ruke. Radiološkim snimanjem otkrivena je jasno ograničena, neinfiltrativna tumorska masa mekih tkiva dimenzija približno 19×13 cm. Biopsija promjene sugerisala je na tumor mezenhimalnog porijekla, nakon čega je izvedena hirurška ekscizija. Histopatološka i imunohistohemijska analiza potvrdile su dijagnozu miofibroblastoma. Pacijentica se nakon operacije oporaviola bez komplikacija i ostaje bez znakova bolesti godinu dana nakon zahvata. Zaključak: ovaj slučaj ukazuje na važnost uključivanja miofibroblastoma u diferencijalnu dijagnozu velikih, klinički benignih masa mekih tkiva na netipičnim lokalizacijama. Poznavanje njegovih kliničko-patoloških karakteristika je ključno za izbjegavanje pogrešne dijagnoze i nepotrebnog liječenja. Potpuna hirurška ekscizija je kurativna, a prognoza odlična.

Ključne riječi: miofibroblastom, benigni tumor vretenastih ćelija, mekotkivna neoplazma, tumor torakalnog zida

INTRODUCTION

Myofibroblastoma is a rare benign mesenchymal tumor that was first described in the breast by Wargotz ES, et al. in 1987 (1). It represents a distinctive benign stromal neoplasm of the breast, composed of myofibroblasts and initially noted to be separate from entities like fibromatosis (desmoid tumor). Mammary myofibroblastoma typically occurs in adults, often middle-aged to older males or postmenopausal females, and usually presents as a well-circumscribed, slow-growing, painless breast mass. Histologically, it is characterized by interlacing fascicles of bland spindle cells (myofibroblasts) set in a collagenous to myxoid stroma with varying amounts of adipose tissue. (2). A subtle but distinctive cytologic feature described in some cases is the presence of "coffee bean" nuclear grooves in the tumor cells. Immunohistochemically, myofibroblastoma typically expresses CD34 and often desmin, consistent with myofibroblastic differentiation, while lacking epithelial markers (cytokeratins) and S-100 protein (3). This profile helps distinguish them from other spindle cell lesions. Notably, these tumors are part of a spectrum of benign soft tissue neoplasms that share genetic features – in particular, a deletion on chromosome 13q14 involving the RB1 gene region, a change also seen in spindle cell lipomas (4).

This genetic finding, along with overlapping morphology, indica tes that mammary myofibroblastoma is closely related to spindle cell lipoma and the related entity cellular angiofibroma. While originally recognized in the breast, extramammary presentations of myofibroblastoma (also termed mammary-type myofibroblastoma when outside the breast) have since been documented, though they remain exceedingly uncommon (5). These tumors can occur in various soft tissue locations, often along the embryonic "milk line" extending from the axilla through the thoracic wall to the groin. Reported extramammary sites include the axilla, chest wall, inguinal region, vulva, perineum, and even such unexpected locations as the head and neck region (5). The tumors in extramammary locations usually present as a well-demarcated, mobile soft tissue mass; depending on location and size, they may cause compressive symptoms but typically do not invade adjacent structures (1). Due to the rarity of these lesions, they can pose a diagnostic challenge and are often initially mistaken for more common tumors of the same region. In this text we report a rare case of a rapidly enlarging myofibroblastoma arising in the lateral thoracic wall and axillary region, and discuss its clinical, radiologic, and pathologic features in the context of the existing literature.

CASE REPORT

A 58-year-old female patient presented with a rapidly growing mass in the left lateral thoracic wall and axillary region. Over the course of three months, the patient noted progressive swelling in the armpit and flank area, which began to interfere with arm movement and caused discomfort. On examination, there was a large, well-defined mass occupying the left lateral chest wall extending into the axilla. The overlying skin was intact without discoloration or ulceration. The mass was firm but mobile on deep palpation, and there was mild non-pitting oedema of the left arm, suggestive of lymphatic or venous outflow compression. No axillary lymphadenopathy separate from the mass was detected.

CT angiography of the chest and axilla revealed an encapsulated soft tissue tumor measuring approximately 16 × 8 cm in the lateral thoracic wall/axillary region. The lesion was situated superficial to the rib cage, displacing the adjacent chest wall musculature and reducing the LL diameter of the chest cavity, but not infiltrating the muscle planes or the rib bones.

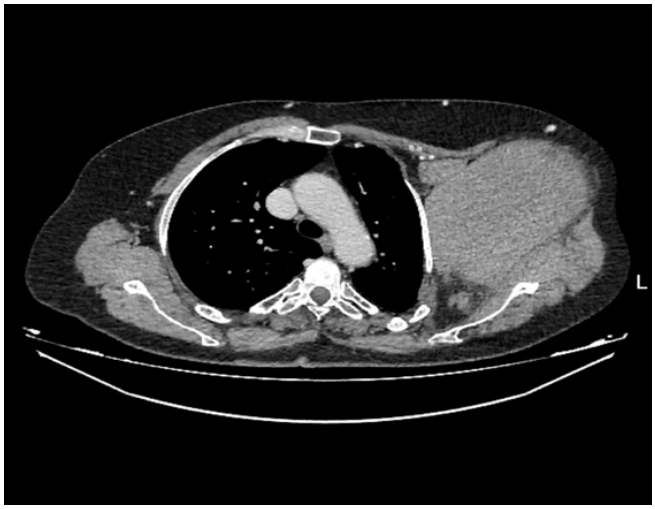

Figure 1 **CT angiography scan of the chest (note that tumor compresses the chest wall but does not invade adjacent structures).**

The mass caused compression of the adjacent axillary vein and lymphatic channels, which correlated with the arm swelling (Figure 1). These imaging characteristics suggested a benign but compressive soft tissue tumor. A differential diagnosis based on imaging included benign spindle cell tumors (such as a fibrous tumor or atypical lipomatous tumor) versus a soft tissue sarcoma; however, the well-circumscribed nature without invasive features favored a benign process.

A core needle biopsy of the mass was performed to establish a diagnosis. Histology from the core biopsy showed a spindle cell neoplasm composed of uniform bland cells arranged in intersecting bundles with interspersed collagen. No significant atypia, necrosis, or high mitotic activity was observed. Immunohistochemical studies on the biopsy showed the lesional spindle cells were positive for vimentin, h caldesmon, CD34, and negative for desmin, pan-cytokeratin, S100, and β-catenin. This immunoprofile indicated a mesenchymal tumor with fibroblastic/myofibroblastic differentiation. Based on these findings, the leading considerations were a benign stromal tumor such as a myofibroblastoma or a solitary fibrous tumor; an aggressive fibromatosis (desmoid tumor) was deemed less likely given the lack of β-catenin expression and circumscribed growth, and a well-differentiated liposarcoma was unlikely due to absence of atypical adipocytes or lipoblasts.

The patient underwent surgical resection of the tumor. An en bloc excision was performed, including the tumor and a rim of adjacent fascia and fat, through an incision along the lateral chest wall and into the axilla. The mass was found to be well-encapsulated, loosely adherent to surrounding adipose tissue but not infiltrating the muscle or axillary vessels. It was successfully delivered in one piece. The resected specimen was a 19.0 × 13.0 × 8.0 cm ovoid mass with a smooth, lobulated external surface.

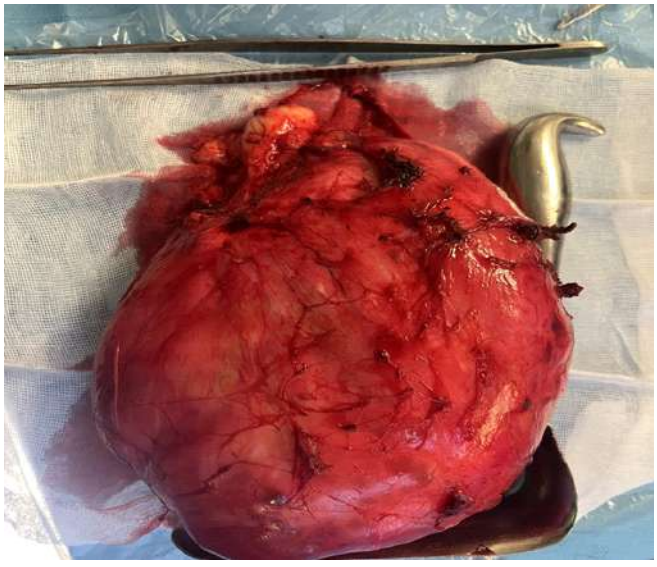

Figure 2 **Resected tumor (picture taken intraoperatively).**

On cut section, the tumor was solid, tan-white with whorled trabeculae, and had focal areas of yellow, suggesting entrapped fat (Figure 2). No hemorrhage or necrosis was grossly apparent.

Microscopic examination of the resected mass confirmed a benign spindle cell neoplasm consistent with myofibroblastoma. The tumor tissue was composed of a hypocellular collagenous stroma. Within the stroma, uniform spindle-shaped cells arranged in a fascicular growth pattern were observed, along with focal areas containing "trapped" mature adipocytes. There was no evidence of cellular or nuclear atypia. Mild perivascular lymphocytic infiltrates were present, accompanied by scattered mast cells. Focal myxoid stromal changes were noted, predominantly in perivascular and subcapsular regions.

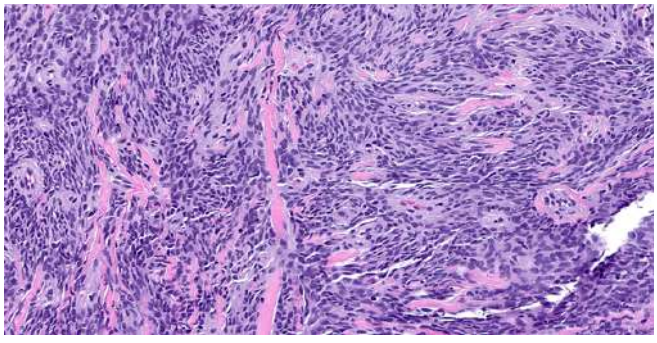

Figure 3 **Pathohistological presentation of the myofibroblastoma (Contributed by Kristen E. Muller, D.O. and Victoria Jones, M.D., M.S.**

The surgical resection margins were free of tumor involvement. There was no evidence of malignancy. The postoperative course was uneventful. The patient's shoulder mobility improved rapidly after surgery, and the arm swelling resolved over a few weeks. At a follow-up visit 6 months after resection, there was no evidence of local recurrence, and the surgical scar was well-healed. The patient had regained full, painless range of motion of the left arm and shoulder. Given the benign nature of myofibroblastoma, no adjuvant therapy was indicated. The plan is for clinical surveillance with periodic physical exams. The patient remains disease-free one year post-operatively.

DISCUSSION

Myofibroblastoma of the breast and its extramammary counterparts are rare tumors that can easily be misdiagnosed preoperatively due to their nonspecific clinical and radiologic appearance. In this case, a rapidly enlarging axillo-thoracic mass in an adult raised concern for a soft tissue sarcoma or other aggressive tumor. Indeed, as seen in this patient, large myofibroblastomas can mimic malignant tumors by virtue of size and rapid growth, yet they generally follow a benign course (6). Our patient's tumor caused compressive symptoms, but importantly it did not invade surrounding structures, a feature that is characteristic of benign myofibroblastomas and contrasts with desmoid-type fibromatosis or high-grade sarcomas (7). This case adds to the limited literature on extramammary myofibroblastoma arising in the torso (thoracic wall/axilla). To date, only a few dozen cases of extramammary myofibroblastomas have been reported in the English literature (8). In a 2015 review of soft tissue myofibroblastoma, 20 cases outside the breast had been described up to that time (9). Those tumors most frequently arose along the embryonic milk line, especially in the inguinal/groin region (the most common site for extramammary myofibroblastoma). Other reported locations include the vulva, perineal region (including perianal area), thigh, knee/popliteal fossa, paratesticular tissue, and even the head and neck region. (10). A recent case report and literature review documented an extremely unusual visceral occurrence of myofibroblastoma in the liver, highlighting that while most of these tumors arise in subcutaneous or superficial soft tissue along the milk line, exceptionally they can appear in abdominal cavity as well (11). Similar cases of axillary or chest wall myofibroblastomas as presented in this case report are rare but have been mentioned in literature reviews of mammary-type myofibroblastomas (12). The primary challenge in diagnosing myofibroblastoma in an unusual location is distinguishing it from other spindle cell tumors. Clinically and radiologically, a myofibroblastoma can be mistaken for a soft tissue sarcoma when large or for an aggressive fibromatosis if it arises in the chest wall. In our case, the well-defined margins on imaging and lack of invasiveness pointed toward a benign process, but only histopathology could provide a definitive diagnosis. In practice, immunohistochemistry is crucial for resolving these differential diagnoses. The combination of CD34 positivity and desmin positivity strongly supports myofibroblastoma over most alternatives. Additionally, many mammary-type myofibroblastomas express hormone receptors (ER and PR), reflecting their relationship to mammary stromal tissue, which can provide a clue in the appropriate context

The treatment of choice for myofibroblastoma is complete surgical excision with clear margins. These tumors are well-circumscribed, and simple excision is usually curative. Unlike desmoid tumors, myofibroblastomas have virtually no risk of aggressive local recurrence. In all published cases to date, including those with tumors reaching very large sizes, the behavior has been benign with no metastases and no true recurrences documented (9,13,14). Our patient's outcome was consistent with this benign behavior.

CONCLUSION

In summary, we present a rare case of an extramammary (mammary-type) myofibroblastoma arising in the lateral thoracic wall and axilla, an unusual location for this tumor. The case underlines the importance of considering benign entities in the differential diagnosis of large, rapidly growing soft tissue masses. Awareness of myofibroblastoma in extramammary sites can prevent misdiagnosis and overtreatment.

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Q Fever Endocarditis in a Patient on Chronic Hemodialysis Treatment: Is it Always Subacute?

Q groznica endokarditis kod pacijenata na hroničnom hemodijaliznom tretmanu. Da li je uvijek subakutan?

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ABSTRACT

Introduction: Q fever endocarditis is a chronic bacterial infection caused by Coxiella burnetii, predominantly affecting heart valves, especially prosthetic ones. Although rare, it presents a serious clinical challenge due to difficulties in both, diagnosis and treatment. Patients undergoing hemodialysis are particularly susceptible to opportunistic infections due to compromised immune function. Case report: we present a case of a patient on chronic hemodialysis diagnosed with mitral valve endocarditis caused by Q fever. This report emphasizes the diagnostic journey, the therapeutic approach, and the patient's treatment course. Q fever endocarditis remains a diagnostic and therapeutic challenge, particularly in immunocompromised populations such as patients undergoing chronic hemodialysis. The subacute clinical presentation often leads to delayed recognition and therefore contributes to difficulties in establishing and managing appropriate therapy. Although standard treatment typically involves prolonged therapy, especially when valve replacement is not performed, there are similar case reports demonstrating successful outcomes with shorter treatment durations. Conclusion this case highlights the importance of individualized therapy in managing complex infections in patients with renal failure. Further research is essential to establish the optimal duration and composition of antimicrobial therapy to enhance treatment outcomes in this vulnerable population

Keywords: Q fever, coxiella burnetti, endocarditis, hemodialysis

SAŽETAK

Uvod: endokarditis izazvan Q groznicom je hronična bakterijska infekcija uzrokovana Coxiella burnetii, koja pretežno zahvata srčane valvule, naročito protetske. Iako rijetka, ova infekcija predstavlja ozbiljan klinički izazov zbog teškoća u dijagnostici i liječenju. Pacijenti na hemodijalizi su posebno podložni oportunim infekcijama zbog oslabljenog imunološkog sistema. Prikaz slučaja: predstavljamo slučaj pacijenta na hroničnoj hemodijalizi kod kojeg je dijagnosticiran endokarditis mitralne valvule izazvan Q groznicom. Ovaj izvještaj naglašava dijagnostički proces, terapijski pristup i tok liječenja pacijenta. Endokarditis uzrokovan Q groznicom i dalje predstavlja dijagnostički i terapijski izazov, naročito kod imunokompromitovanih pacijenata poput onih na hroničnoj hemodijalizi. Subakutna klinička slika često dovodi do odgođenog prepoznavanja, što dodatno otežava uspostavljanje i sprovođenje adekvatne terapije. Iako standardno liječenje podrazumijeva produženu terapiju, posebno kada se ne vrši zamjena valvule, postoje izvještaji o sličnim slučajevima sa uspješnim ishodom i uz kraće trajanje liječenja. Zaključak: ovaj slučaj ističe važnost individualizovanog pristupa terapiji u liječenju kompleksnih infekcija kod pacijenata sa bubrežnim zatajenjem. Neophodna su dodatna istraživanja kako bi se utvrdilo optimalno trajanje i sastav antimikrobne terapije u cilju poboljšanja ishoda liječenja u ovoj ranjivoj populaciji.

Ključne riječi: Q groznica, coxiella burnetti, endokarditis, hemodijaliza

INTRODUCTION

Q fever is caused by a gram-negative bacterium Coxiella burnetii and typically it causes an influenza-like illness with fever, headache, myalgia and fatigue. It is a zoonotic infection involving both domestic and wild animals such as cattle or sheep which act as reservoirs for the organism (1).

Rarely, Q fever causes more localized infections of which the most commonly described and significant is endocarditis (2). As a cause of endocarditis, Q fever presents a diagnostic challenge as Coxiella burnetii does not grow on routine laboratory cultures and valvular vegetations are small and rarely seen with echocardiography (2,3). Coxiella burnetii is an intracellular bacterium that multiplies within the acidic environment of phagolysosomes which reduces the effectiveness of antibiotics against it (4,5).

Dialysis is a life-sustaining treatment for individuals with kidney failure, where the kidneys can no longer effectively filter waste and excess fluids from the blood. There are two types of dialysis: hemodialysis, which uses a machine to filter blood outside the body, and peritoneal dialysis, which utilizes the lining of the abdomen to filter blood internally (6).

Patients undergoing dialysis often face challenges such as strict dietary restrictions, fluid intake limitations, and increased risk of complications like infections and cardiovascular issues. Managing these patients requires a multidisciplinary approach, including regular monitoring, medication management, and lifestyle modifications to improve quality of life and outcomes (7,8).

CASE REPORT

We present a case of a 65-year-old patient undergoing chronic hemodialysis treatment, who was diagnosed with mitral valve endocarditis caused by the bacterium Coxiella burnetii. The patient was hospitalized due to an unclear febrile condition ten days prior to admission to the Clinic of Infectious Diseases. The fevers were accompanied by chills and shivering, and according to a heteroanamnestic report, the patient appeared confused during episodes of shivering. He denied any other symptoms related to other organ systems.

Medical history

A long-term hypertensive patient, on chronic hemodialysis treatment for eleven years, underwent cholecystectomy five years ago. He lives with his wife and two sons, both married with families, in a modest house. He reports an epidemiological detail that he owned 40 cows, which were under veterinary supervision and vaccinated against current diseases.

Clinical status on the day of admission showed a patient with a larger musculoskeletal build, conscious, communicative, oriented, eupneic at rest, with clear skin, afebrile, and both cardiopulmonary and respiratory systems compensated. No edema or deformities in the extremities; neurologically intact. An AV fistula was placed in the left cubital region.

Basic lab findings

In the hematology profile, the following parameters were pathological: Leukocytes 14.80 x109/L, Erythrocytes 3.17 x10^{12}/L, Hemoglobin 107 g/L, Hematocrit 33%, MCV 104 fL, Platelets 441 x109/L. The following parameters are normal in this section: MCH 34 pg, MCHC 327 g/L, MPV 9.9 Fl. In the differential blood count DBC, Neutrophilic granulocytes are elevated: 11.30 x109/L, while others parameters are within normal range: Lymphocytes 2.2 x109/L, Monocytes 0.9 x109/L, Eosinophilic granulocytes 0.30 x109/L, Basophilic granulocytes 0.00 x109/L.

Pathological findings in clinical biochemistry include: Potassium 5.6 mmol/L, Magnesium 1.27 mmol/L, Phosphorus 2.0 mmol/L, Urea 23.0 mmol/L, Creatinine 930 µmol/L, AST 106 U/L, ALT 136 U/L, CRP 303.8 mg/L, Troponin 48 ng/L, Gamma GT 364 U/L, CKMB * U/L, Ferritin 2587.04 ng/ml, CRP 321.0 mg/L. Normal parameters include: Sodium 136 mmol/L, Calcium 2.44 mmol/L, Chlorides 105 mmol/L, LDH 232 U/L and CK 15 U/L. In Proteins profile, Albumin is only decreased at 27 g/ while other parameters are within normal range: Total proteins 64 g/L, Globulins 37 g/L, Oligoclonal traces Albumin 27 g/L.

Other diagnostic findings

In a patient undergoing hemodialysis treatment, the initial chest X-ray showed bilateral pleural effusion. Diagnostics was complemented by a CT scan which indicated minimal pleural effusion without significant pathological findings (Figure 1,2,3). Upon admission, empirical dual antimicrobial therapy (imipenem/cilastatin and vancomycin) was initiated, along with ongoing diagnostic and microbiological investigations. Serological testing confirmed a subacute form of Q fever complicated by mitral valve endocarditis, which was verified by transthoracic echocardiography (vegetation measuring 1.8 x 1 cm).

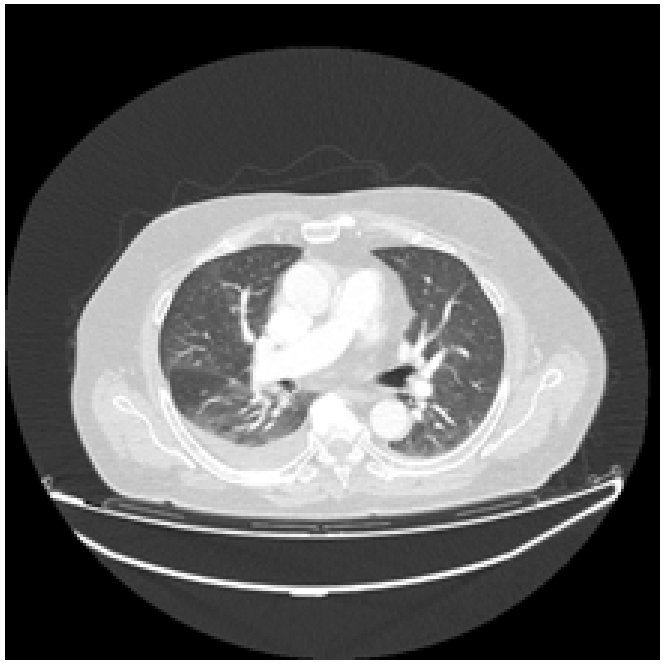

Figure 1 **Chest computed tomography showed minimal right-sided pleural effusion.**

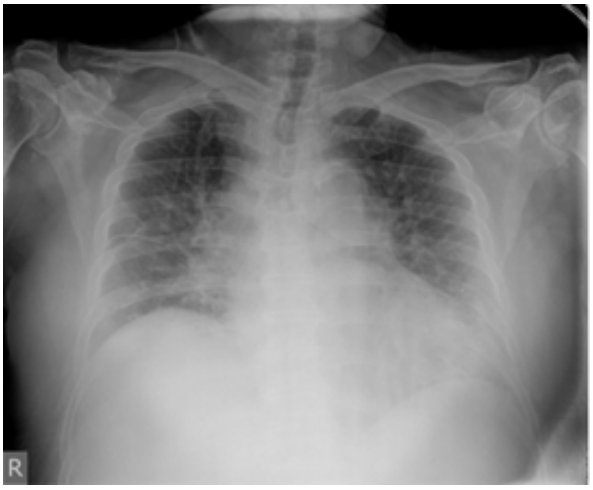

Figure 2 **Initial Chest X-ray showed right and left sided pleural effusion.**

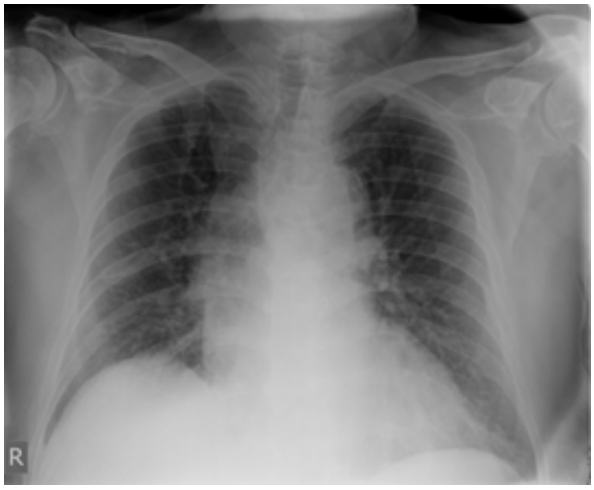

Figure 3 **Chest X-ray while the treatment.**

Therapy was adjusted based on microbiological findings and included a combination of vancomycin, imipenem, doxycycline, ciprofloxacin, and rifampicin. During hospitalization, the patient experienced paroxysmal tachycardia and atrial fibrillation, accompanied by episodes of orthopnea. Treatment was conducted in a multidisciplinary manner with consultations from a cardiologist, cardiac surgeon, thoracic surgeon, and nephrologist.

The patient underwent daily hemodialysis outside the regular schedule until his condition stabilized. In the final week of hospitalization, he was hemodynamically stable, mobile, and functional. However, during one dialysis session, he developed supraventricular tachycardia with atrial fibrillation, which was treated with a Cordarone infusion.

In the final phase of hospitalization, the patient suffered a sudden cardiac arrest. Death was confirmed by the attending physicians.

DISCUSSION

Q fever, caused by the obligate intracellular bacterium Coxiella burnetii, presents a significant challenge in diagnosis and treatment, particularly when it progresses to its chronic form, which most commonly manifests as endocarditis. Although in most cases the disease follows a subacute course, its presentation can be vague and nonspecific, further complicating timely diagnosis, especially in patients with comorbidities such as renal insufficiency and immunosuppression (9,10).

While Vizinho R, et al. emphasized early treatment with doxycy cline and hydroxychloroquine in their cases, where both patients were on hemodialysis and presented with nonspecific symptoms such as recurrent fever, anemia, and immunosuppression, they highlighted the importance of timely clinical suspicion and serologic testing (10).

In our case, the patient was undergoing chronic hemodialysis, which in itself was a significant risk factor for the development of infections, including infective endocarditis (11). The initial clinical presentation was nonspecific minimal pleural effusion, fever, shortness of breath, and orthopnea. However, the diagnosis of chronic Q fever complicated by mitral valve endocarditis was made only after serological testing and echocardiography, which revealed a vegetation measuring 1.8 x 1 cm (9).

Unlike our case, in which the diagnosis was made only after serological tests and the appearance of vegetation, in the patient described by the authors from Spain, Q fever was considered earlier during the evaluation of the febrile condition, thus preventing progression to a complicated form of the disease (12).

Diagnosis of endocarditis in most patients with Q fever is often delayed-on average up to eight months after the onset of symptoms-attributable to nonspecific presentation, negative blood cultures, and a low index of suspicion among clinicians (9,13). Similar delays have been reported in patients on dialysis programs, highlighting the need for a higher degree of clinical suspicion for Q fever in these patients (12,10).

In our patient, broad-spectrum antimicrobial therapy (imipenem/cilastatin, vancomycin) was initiated empirically and later adjusted based on microbiological findings (doxycycline, ciprofloxacin, rifampicin). Although the standard therapy for Q fever endocarditis (doxycycline + hydroxychloroquine) was not administered, a multidisciplinary approach including a cardiologist, cardiac surgeon, thoracic surgeon, and nephrologist enabled temporary stabilization of the patient. This therapeutic strategy, although outside the standard regimen, reflects the complexity of treating patients with concurrent acute and chronic illnesses (14,15).

Heydari AA, et al. described a patient with Q fever endocarditis who did not exhibit significant cardiac failure, thanks to the timely administration of combination therapy (doxycycline + hydroxychloroquine), a favorable outcome was achieved without surgical intervention (13).

Unfortunately, despite initial stabilization, the outcome was unfavorable. During one of the hemodialysis sessions, the patient experienced supraventricular tachycardia and atrial fibrillation, followed by sudden cardiac arrest. Mortality in patients with native valves affected by Q fever endocarditis reaches up to 28%, while it significantly decreases (below 5%) in those who receive appropriate long-term combination therapy (14).

It is also important to note that Q fever is often unrecognized in dialysis centers, and some studies suggest a significant underdiagnosis of the chronic form of the disease in this population (12,10). In this context, serological screening for Coxiella burnetii should be considered in patients with unexplained febrile states, anemia resistant to therapy, and previously known heart conditions, particularly in those undergoing chronic hemodialysis treatment (16).

CONCLUSION

This case highlights the importance of individualized therapy in managing complex infections in patients with renal failure. Further research is essential to establish the optimal duration and composition of antimicrobial therapy to enhance treatment outcomes in this vulnerable population.

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A Management Challenge of Morel - Lavallée Lesion in a 38-Year-Old Male Patient

Izazov u tretmanu Morel - Lavallée lezije kod 38-godišnjeg pacijenta

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ABSTRACT

Introduction: Morel-Lavallée lesions are post-traumatic, closed degloving injuries occurring deep to subcutaneous plane due to disruption of capillaries resulting in an effusion containing hemolymph and necrotic fat. Case report: a 38-years old male patient is presented with ultrasound verified Morel-Lavallée lesion after injury of the thigh caused by heavy object falling onto it. The patient was initially treated conservatively. After unsuccessful conservative management, surgical treatment was performed. Conclusion: postoperative follow-up showed that surgical treatment was correct and successful choice which allowed patient to have improved quality of life.

Keywords: Morel-Lavallée lesion, degloving injuries

SAŽETAK

Uvod: Morel-Lavallée lezije su posttraumatske, zatvorene, raslojavajuće povrede koje nastaju duboko ispod potkožnog sloja usljed prekida kapilara, što dovodi do nakupljanja tečnosti koja sadrži hemolimfu i nekrotično masno tkivo. Prikaz slučaja: 38-godišnji pacijent se javio na pregled sa ultrzavučno potvrđenom Morel-Lavallée lezijom nakon povrede natkoljenice uzrokovane padom teškog tereta na istu. Inicijalno je pacijent tretiran konzervativno. Nakon neuspješnog konzervativnog tretmana, donesena je odluka o hirurškom tretmanu. Zaključak: postoperativno praćenje pacijenta je pokazalo da je hirurški tretman bio ispravan i uspješan izbor koji je pacijentu omogućio poboljšan kvalitet života.

Ključne riječi: Morel-Lavallée lezija, raslojavajuće povrede

INTRODUCTION

Morel - Lavallée Lesions (MLL) are uncommon shearing injuries resulting in separation of the skin and subcutaneous tissue from the underlying fascia - closed internal degloving injuries, classically occurring around the greater trochanter (30.4%), pelvis (18.6%), thigh (20.1%), knee joint (15.7%), gluteal region (6.4%), lumbosacral area (3.4%), abdominal area (1.4%), lower leg (1.5%) and on the head (0.5%) (1), but can appear elsewhere as well (2) (Figure 1). The impact of devastating trauma leads to the injury of lymphatics and blood vessels that lie in the vicinity, resulting in the accumulation of lymph and blood in this potential space. This results in the setting of a chronic inflammatory reaction, which later leads to the formation of a capsulated lesion lined by a fibrous capsule and filled with necrotic fatty tissue, blood products, fibrin, and debris (3). The Morel-Lavallée lesion clinically presents as a painful fluctuant swelling at the site of involvement. The lesion is also called as Morel-Lavallée seroma, posttraumatic soft tissue cyst, post-traumatic extravasation or Morel-Lavallée effusion (4). The diagnosis is generally made on the physical examination. However, radiological investigations can help when clinical suspicion arises. The investigation of choice for this lesion is Magnetic Resonance Imaging, as it defines various parameters of the injury, including size, shape, contents, and its chronicity, but it is rarely required for the diagnosis (5). Herein, we report a case of Morel-Lavallée lesion in a 38-years old male patient which is successfully diagnosed by an ultrasound.

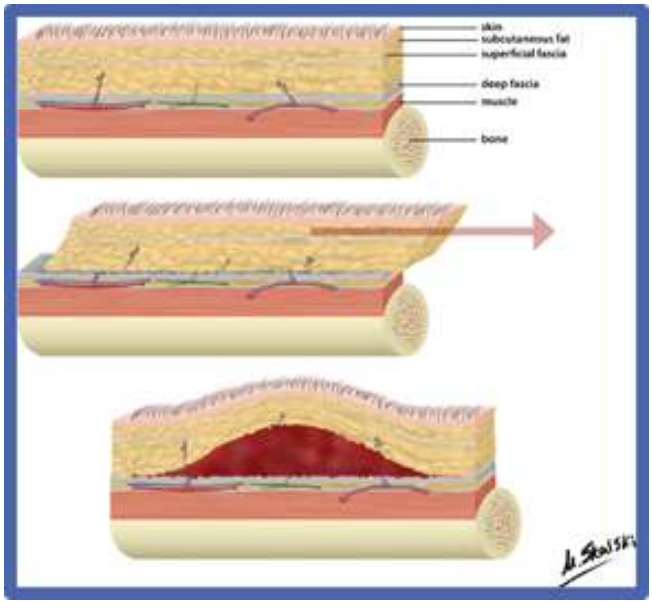

Figure 1 **Illustration presents a cross-section of tissue from the skin to bone demonstrating the effect of a Morel-Lavallée lesion (MLL).**
(https://radiopaedia.org/cases/morel-Lavallée-lesion-illustration)

CASE REPORT

A 38-years old male patient reported to the Clinic of Orthopedics and Traumatology of the Clinical Center University of Sarajevo after right upper leg injury which had been sustained after a heavy object fell onto it. The clinical examination showed swelling and hematoma located on the medial side of the right knee joint, 10cm above the level of patella. Since the X-ray imaging did not show any bone fracture, ultrasound was performed. The ultrasound examination revealed fluid collection visible in the subcutaneous fat tissue at a depth of 2 cm from the skin surface, with a transverse diameter of 1.5 cm, accompanied by oedema of the surrounding fat tissue. The emergency punction was performed showing approximately 90 mililitres of the evacuated hemorrhagic collection. Due to the persistent swelling, repeated subcutaneous aspiration was accomplished and 20 milliliters of hemorrhagic fluid were drained. During the next follow-up examination new ultrasound of the thigh showed a huge fluid collection located ventromedially in the subcutaneous fat tissue, extrafascially, with the cranio-caudal diameter of 25 cm, a latero-lateral diameter of 15 cm, and a depth of up to 3.5 cm without communication with the knee joint. Based on the echographic characteristics, this appears to be a Morel-Lavallée seroma resulting from trauma or rupture of the fat tissue (Figure 2).

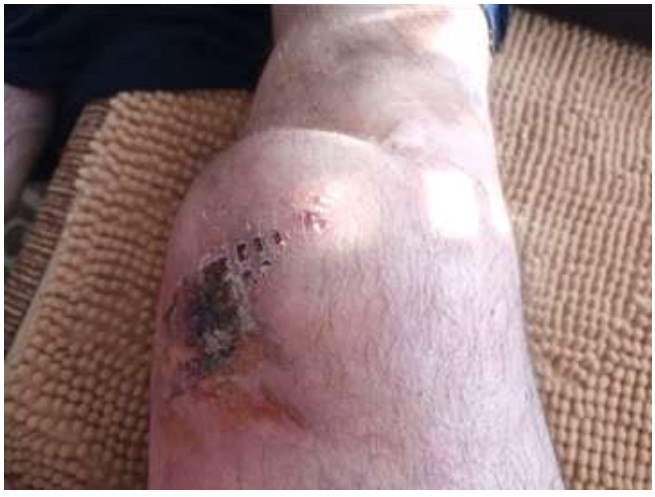

Figure 2 **The clinical examination at the follow-up visit.**

In the following three examinations the swelling persisted and nearly 2 liters of hemorrhagic fluid were evacuated. Furthermore, an incision was made at the site of the oedema and a drain was placed. Since there was no clinical improvement at the next appointment, a decision was made to admit the patient for surgical treatment. Upon the patient's admission, antibiotic prophylaxis and thromboprophylaxis were initiated. The patient underwent surgical treatment under spinal anesthesia. Intraoperatively, a large amount of unorganized hematoma was found beneath the necrotic subcutaneous fat tissue, along with the presence of a fibrous capsule. The muscle fascia was intact. The hematoma was completely evacuated. The fibrous capsule was removed. Debridement was performed and an aspiration drain was placed. The wound was regularly dressed and a significant improvement in the clinical condition was noted. Upon discharge, at the follow-up examination, there were no signs of fluctuation in the projection of the right thigh, with the presence of local induration (Figure 3). The follow-up ultrasound was required, which showed no isolated fluid collections in the specified region.

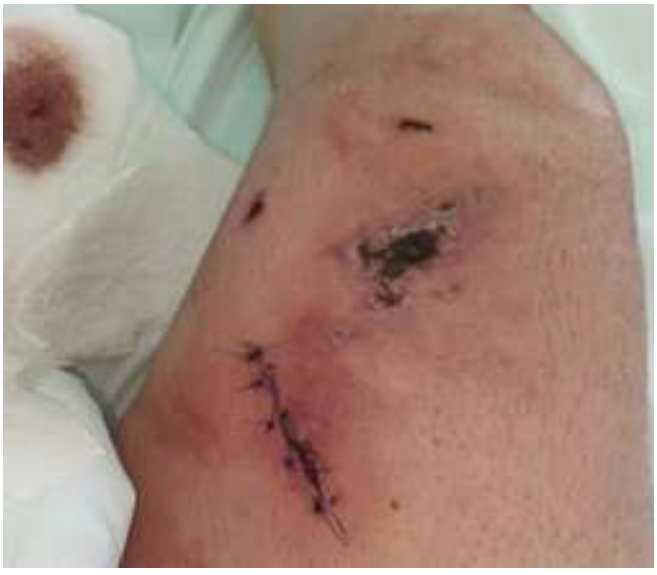

Figure 3 **The clinical examination at the first control appointment.**

The patient was referred for physical therapy. After completing the physical therapy, no subjective complaints were reported. The clinical examination was entirely normal (Figure 4).

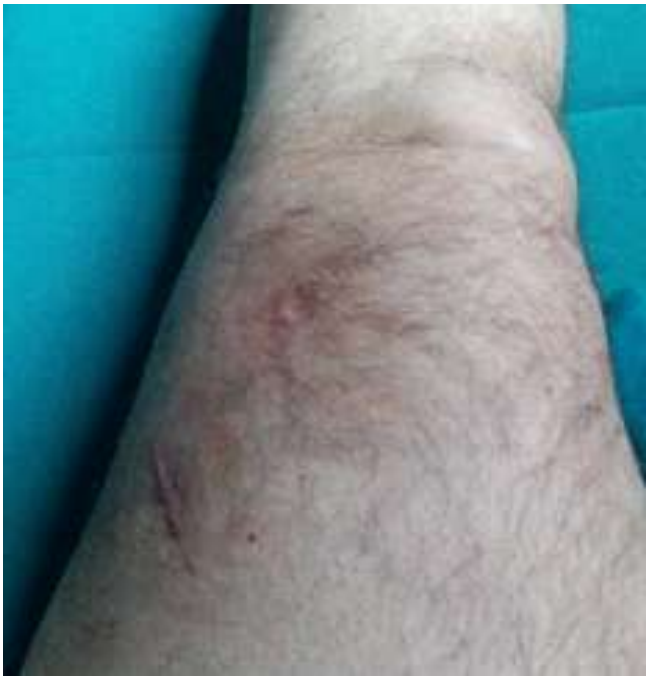

Figure 4 **Clinical examination was entirely normal after surgical treatment and physical therapy.**

The patient has returned to daily activities. There was no need for further follow-up examinations.

DISCUSSION

The Morel-Lavallée lesion is a rare pathological condition that was first described in the mid-1800s (6). It occurs after a traumatic incident where the subcutaneous soft tissues are separated from the deeper fascial layer creating a potential cavity (6). Although this lesion most commonly occurs in the projection of the trochanteric region of the hip, it can also occur at other locations such as the distal thigh and knee, as demonstrated in this case report. MLLs can have a delayed diagnosis or misdiagnosis (7). Kottmeir S, et al., reported that MLLs are diagnostically missed up to 44% of the time (8). Delayed diagnosis and treatment of MLLs can cause an inflammatory response in the soft tissues and form a fibrous capsule around the fluid (9). This capsule is thought to inhibit the absorption of the fluid and aids in the re-accumulation of fluid after percutaneous drainage as was seen with the present case (9). Therapeutic options may vary, ranging from conservative to surgical treatment modalities. If this lesion remains unrecognized, it can lead to infections and skin necrosis (3). If the lesion is diagnosed in the initial stages without the fibrous capsule, conservative treatment methods may be used including compression, nonsteroidal anti-inflammatory drugs and physical therapy (3). If a fibrous capsule is formed, therapeutic options may range from percutaneous aspiration of the contents to the surgical treatment and excision (3). In our case, percutaneous aspiration and incision at the site of the hematoma were unsuccessful and the patient underwent surgical treatment after which a complete recovery was achieved.

CONCLUSION

In this article, a case of Morel-Lavallée lesion is presented in a 38-year-old male patient, which occurred following a trauma to the right thigh after the fall of a heavy object onto it. The diagnosis was made using ultrasound. Therapeutic modalities for Morel-Lavallée lesions range from conservative to surgical treatment. In our case, the patient was initially treated conservatively and using minimal invasive technique such as percutaneous aspiration and inicision at the site of hematoma. Considering the formation of a fibrous capsule, as verified by ultrasound, and the clinical deterioration in terms of hematoma progression, surgical treatment was indicated. Following surgical treatment, there was complete regression of symptoms and local findings, and the patient returned to daily activities.

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Elective Caesarean Section in a Term Pregnancy Complicated by Primary Myelofibrosis and Splenomegaly

Elektivni carski rez u terminskoj trudnoći komplikovanoj primarnom mijelofibrozom i splenomegalijom

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ABSTRACT

Introduction: pregnancy in patients with myelofibrosis repre sents a significant clinical challenge due to the disease's effects and increased risk of maternal thrombosis, hemorrhage, and placental dysfunction. Myelofibrosis is the least common in women of reproductive age, accounting for approximately ten to twenty percent of cases worldwide. Case report: a 37-year-old second gravida woman, previously diagnosed with primary myelofibrosis and possible essential thrombocythemia, presented a challenge due to managing massive splenomegaly, thrombophilia, and the risks associated with delivery, emphasizing the importance of individualized care and collaborative decision-making regarding the delivery planning. Discussion: fertility counseling should be provided to all young women with a confirmed diagnosis of MPN. However, MPN is discovered during pregnancy in 20% to 30% of cases. As a result, a risk-adjusted treatment strategy is indicated, taking into account the obstetric history and the risk of thrombosis. Conclusion: optimal outcomes depend on coordinated, multidisciplinary care involving hematologists, obstetricians, and anesthesiologists. Regular monitoring, individualized treatment planning, and timely delivery decisions are critical to ensure maternal and neonatal safety in this high-risk population.

Keywords: pregnancy, myelofibrosis, splenomegaly, caeserean section

SAŽETAK

Uvod: trudnoća kod pacijentica sa mijelofibrozom predstavlja značajan klinički izazov zbog učinka bolesti i povećanog rizika od majčine tromboze, krvarenja i disfunkcije placente. Mijelofibroza se rijetko javlja kod žena reproduktivne dobi, čineći otprilike deset do dvadeset posto slučajeva u svijetu. Prikaz slučaja: 37-godišnja drugorotka, kojoj je prethodno dijagnosticirana primarna mijelofibroza i moguća esencijalna trombocitemija, predstavlja veliki klinički izazov zbog masivne splenomegalije, trombofilije i potencijalnih rizika povezanima s porodom, pritom naglašavajući važnost individualiziranog tretmana i zajedničkog donošenja odluka u vezi s planiranjem poroda. Diskusija: savjetovanje o plodnosti treba pružiti svim mladim ženama kojima je potvrđena dijagnoza mijelofibroze. Na žalost otkrije se tek tijekom trudnoće u 20% do 30% slučajeva. Kao rezultat toga, indicirana je strategija liječenja prilagođena riziku, uzimajući u obzir opstetričku anamnezu i rizik od tromboze. Zaključak: optimalni ishodi ovise o koordiniranom, multidisciplinarnom tretmanu koja uključuje hematologe, opstetričare i anesteziologe. Redovito praćenje, individualizirano planiranje liječenja i pravovremene odluke o porodu ključni su za očuvanje sigurnosti porodilja i novorođenčadi u ovoj visokorizičnoj populaciji.

Ključne riječi: trudnoća, mijelofibroza, splenomegalija, carski rez

INTRODUCTION

Pregnancy in patients with myelofibrosis represents a significant clinical challenge due to the disease's effects and increased risk of maternal thrombosis, hemorrhage, and placental dysfunction (1).

Myeloproliferative neoplasms (MPNs) are a diverse collection of clonal hematopoietic stem cell disorders defined by excessive proliferation of one or more myeloid lineages in the bone marrow. MPN classification and diagnostic criteria have changed significantly over the years, reflecting increasing recognition of these disorders and improved comprehension of their biology and clinical-pathological characteristics. The current World Health Organization (WHO) Classification recognizes four major sub-groups of MPNs: (I) Chronic Myeloid Leukemia; (II) classical Philadelphia-negative MPNs (Polycythemia Vera; Essential Thrombocythemia; Primary Myelofibrosis); (III) non-classical Philadelphia-negative MPNs (Chronic Neutrophilic Leukemia; Chronic Eosinophilic Leukemia); and (IV) MPNs, unclassifiable (MPN-U) (1).

Myelofibrosis is the least common in women of reproductive age, accounting for approximately ten to twenty percent of cases worldwide. MPNs are more commonly found in middle-aged and elderly individuals (2).

These hematological disorders are characterized by excessive hematopoiesis and the overproduction of mature differentiated blood cells. Main characteristics of myeloproliferative disorders are predisposition to thrombosis, hemorrhage, progression to myelofibrosis, and acute myeloid leukemia (3).

These associated conditions are controlled by pregnancy's prothrombotic potential, which results in alterations in hemostatic factors and prothrombotic proteins as well as affects the physical mechanism of venous blood flow. Thrombosis is one of the primary causes of maternal morbidity, according to recent maternal mortality investigations (4).

Pregnancies with myelofibrosis are a challenge for obstetricians and involve significant risks for both the mother and the fetus. The normal course of pregnancy is determined by the establishment and maintenance of regular uterine blood flow, as well as, implicitly, appropriate placental development. Pregnancy is a hypercoagulable state and when it is combined with a myeloproliferative condition, a severe prothrombotic status is established. Additionally, there are risks of placental thrombosis, fetal growth restriction or fetal death, and maternal thrombosis (5).

An early indicator of placental dysfunction is represented by abnormal placental invasion of the maternal spiral arteries. Thrombotic obstruction of placental circulation may be a later marker of placental malfunction. These warning signs are critical in the context of concerns caused by placental dysfunction, including placental abruption, intrauterine growth restriction, and preeclampsia. In myeloproliferative disorders, the prothrombotic condition is caused by a combination of blood rheology, potential leukocyte adhesion, platelet activation, thrombocytosis, and platelet-leukocyte aggregates. Any prior thrombotic or hemorrhagic event, unexplained recurrent loss during the first trimester, intrauterine growth restriction, intrauterine death, stillbirth, placental abruption, severe preeclampsia, or significant antepartum or postpartum hemorrhage in the patient's medical history worsens the prognosis of pregnancy (5). Splenomegaly, a defining feature of myelofibrosis, might be especially problematic during pregnancy. As the spleen enlarges, it can cause abdominal discomfort, mechanical pressure on the uterus, and, in rare cases, spontaneous rupture. Patients usually experience debilitating symptoms such as pain and early satiety, in addition to cellular sequestration that causes severe cytopenias (6).

AIM

The aim of the paper was to represent the case of pregnancy in a patient with myelofibrosis which continues to remain high-risk, requiring careful coordination and specialized management to address the overlapping challenges of disease and gestation.

CASE REPORT

A 37-year-old second gravida woman, previously diagnosed with primary myelofibrosis and possible essential thrombocythemia, was referred to the Clinic of Gynecology and Obstetrics of the Clinical Center University of Sarajevo at 36 weeks of gestation for consultation and further evaluation regarding pregnancy termination and delivery planning.

She reported regular menstrual cycles, with menarche at the age of 12. Her reproductive history included one spontaneous abortion and one vaginal delivery. Tragically, her son passed away due to sagittal sinus thrombosis and intracranial hemorrhage, as reported by the patient.

The diagnostic evaluation for myelofibrosis was initiated when she reported severe pain in the left upper abdominal quadrant and accordinly admitted to the Clinic of Emergency Medicine of the same institution. Abdominal ultrasonography revealed significant splenomegaly, with the spleen measuring approximately 16 cm in diameter. Based on these findings and clinical suspicion, she was referred to the hematologist for further investigations.

Thrombophilia screening revealed heterozygosity for the methylenetetrahydrofolate reductase (MTHFR) 1273 gene mutation, as well as Protein S deficiency. These findings prompted further laboratory investigations, raising suspicion for an underlying myeloproliferative neoplasm. Tests included D-dimer, erythropoietin, INR, APTT, antithrombin (AT), serum protein electrophoresis and immunofixation, homocysteine, ferritin, fibrinogen, peripheral smear, lupus anticoagulant (LA), and neoplastic plasma cell analysis.

PCR testing for JAK2, CALR, and MPL mutations returned negative, which assisted in the classification of her myeloproliferative disorder. A bone marrow biopsy revealed morphological features consistent with a myeloproliferative neoplasm. Correlating with laboratory findings, the main differential diagnosis included essential thrombocythemia and the prefibrotic stage of primary myelofibrosis. Before conception, an abdominal ultrasound revealed progressive splenomegaly, with the spleen measuring approximately 20 cm in diameter. The patient occasionally reported mild abdominal discomfort, general malaise, and intermittent numbness in her hands.

Upon confirmation of pregnancy, antenatal care was initiated under the supervision of her primary care gynecologist, in coordination with a consulting hematologist. The patient was maintained on a regimen that included methylfolate 400 µg (twice weekly), methylcobalamin 1000 µg (once weekly), acetylsalicylic acid 100 mg daily, and vitamin D 2000 IU daily.

Her hematologist recommended regular monitoring of coagulation parameters, including D-dimer, activated partial thromboplastin time (aPTT), and international normalized ratio (INR), at intervals of approximately every 3-4 weeks. Throughout the pregnancy, these values remained within normal reference ranges. Additionally, a non-invasive prenatal test (NIPT) was performed, yielding negative results for common chromosomal abnormalities, including trisomies 21, 18, and 13, as well as sex chromosome aneuploidies, rare autosomal aneuploidies, and selected microdeletions and duplications.

An obstetric ultrasound was performed in our clinic at 36 weeks of gestation. The fetus was in cephalic presentation. The placenta was posteriorly located, with no signs of previa or abruption. The amniotic fluid index was within normal values. Umbilical artery Doppler assessment showed a resistance index (RI) of 0.55, consistent with normal placental perfusion.

Fetal biometric measurements were as follows: biparietal diameter (BPD): 88 mm, head circumference (HC): 323 mm, abdominal circumference (AC): 308 mm, and femur length (FL): 72 mm. The estimated fetal weight (EFW) was approximately 3100 grams. Fetal heart rate was normal, and spontaneous fetal movements were observed during the examination. No structural anomalies were detected.

By delivery time, follow-up abdominal ultrasound imaging showed further splenic enlargement, with the spleen reaching a diameter of 24.2 cm. The hematologist did not advise vaginal delivery due to a significantly increased risk of splenic rupture associated with its enlargement. A planned caesarean section was recommended if coagulation parameters, including INR, aPTT, and number of thrombocytes, remained within safe reference ranges.

Table 1 **Laboratory values.**

Parameter	*Result*	*Reference Range*	*Unit*
Thrombocytes	**200**	**158 - 424**	**×10⁹/L**
INR	**0.98**	**0.80 - 1.20**	
APTT	**28.00**	**25.9 - 36.6**	**Sec**

As all laboratory parameters were within the acceptable range, an elective caesarean section was recommended as the preferred mode of delivery.

At 38 weeks and 5 days of gestation, an elective cesarean section was performed under spinal anesthesia. A suprapubic transverse laparotomy was carried out using a Pfannenstiel incision. A healthy full-term female neonate was delivered, weighing 3350 grams and measuring 51 cm in length, with an Apgar score of 10 at both one and five minutes. The newborn was handed over to the attending neonatologist for routine postnatal evaluation and care. Both the mother and newborn had stable postoperative courses and were discharged on the third postoperative day. The patient was hemodynamically stable, normotensive, afebrile, and eupneic. In coordination with the hematologist, postpartum anticoagulation with enoxaparin sodium 40 mg (subcutaneously once daily) was prescribed for the next 4-6 weeks. The 10-day postpartum follow-up was without any complaints. On physical examination, the abdomen was soft, non-tender, and without signs of infection or complications. The surgical incision was healing well. Lactation was successfully established. The postoperative course and delivery were uneventful. She was counseled on the importance of continued hematologic follow-up for long-term management of her underlying primary myelofibrosis.

DISCUSSION

Although myeloproliferative neoplasms (MPNs) are typically considered diseases of older adults, as they are often diagnosed in the sixth or seventh decade of life, they may also occur in younger individuals. Consequently, pregnancy in patients with MPNs, while uncommon, presents a significant clinical challenge requiring multidisciplinary management.

Pregnancy itself is a prothrombotic state, and thrombosis remains a leading cause of maternal morbidity and mortality. In patients with MPNs, the risk of thromboembolic events is further amplified, alongside preeclampsia, placental insufficiency, intrauterine growth restriction, and fetal loss. These risks underscore the importance of close monitoring by both hematologists and obstetricians throughout gestation (8).

Primary myelofibrosis (PMF) is a clonal hematologic disorder characterized by chronic myeloproliferation, atypical megakaryocytic hyperplasia, increased bone marrow vascularity, and progressive fibrosis. These pathologic features impair hematopoiesis and often result in anemia, splenomegaly, and extramedullary hematopoiesis. The pathogenesis of PMF is complex and multifactorial, involving chromosomal abnormalities, mutations in the JAK/STAT signaling pathway, dysregulation of megakaryocyte proliferation, elevated cytokine production, and overexpression of thrombopoietin (9).

Despite its rarity in pregnancy, there is a growing need for evidence-based guidance on the management of PMF in pregnant patients. This case highlights the challenges of managing massive splenomegaly, thrombophilia, and the risks associated with delivery, emphasizing the importance of individualized care and collaborative decision-making.

One of the facilitating facts, in this case, was that primary myelofibrosis was diagnosed shortly before conception, and that the mentioned patient was under the supervision and control of her hematologist, who was also involved in the pregnancy's management and played a significant role in the decision on how to terminate the pregnancy, in consultation with the entire team. Unfortunately, this is not always the case, and individuals with these hematological diseases frequently go misdiagnosed, resulting in difficulties, such was the case of pregnancy with polycythemia vera that went undiagnosed for years, which was aggravated postpartum by portal vein occlusion (10).

Other individual cases have been presented, such as the case of a patient with myelofibrosis who got pregnant during ruxolitinib treatment in the first trimester and experienced a successful pregnancy outcome (11).

This emphasizes the importance of fertility counseling. It should be provided to all young women who have a confirmed diagnosis of MPN; however, it is discovered during pregnancy in 20% to 30% of cases. As a result, a risk-adjusted treatment strategy is indicated, taking into account the obstetric history and the risk of thrombosis. Warfarin and hydroxyurea should be avoided because of their teratogenic properties (12). Additionally, the safety of direct oral anticoagulants during pregnancy has not been confirmed. Aspirin 81 mg daily is recommended for all pregnancies, while aspirin twice daily is suggested in situations of JAK2 mutation or the presence of cardiovascular risk factors. Cytoreductive therapy with INF-α is recommended for high-risk individuals with a history of thrombosis. It should also be explored for low-risk patients with poorly managed Hct values, significant splenomegaly. Cytoreductive therapy with INF-α is recommended for high-risk patients with a history of thrombosis, as well as low-risk patients with uncontrolled Hct levels, splenomegaly, or recurrent fetal loss. Antepartum systemic anticoagulation with LMWH is indicated only in patients with a history of venous thrombosis (13).

Overall, there is a lack of evidence on reproductive patterns and fertility in women with MPN. Consequently, preconceptional counseling and optimal therapy are mostly based on retrospective observations and personal experience. Given the wide variation in treatment approaches, there is an urgent need for collaborative initiatives to produce prospective data and create evidence-based care regimens for pregnancies in women with MPN (13).

CONCLUSION

The incidence of pregnancy in patients with MPNs, including PMF, is gradually increasing. These pregnancies are associated with elevated risks of both maternal and fetal complications, particularly thromboembolic events, hypertensive disorders, placental insufficiency, and preterm delivery. Optimal outcomes depend on coordinated, multidisciplinary care involving hematologists, obstetricians, and anesthesiologists. Regular monitoring, individualized treatment planning, and timely delivery decisions are critical to ensure maternal and neonatal safety in this high-risk population.

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Cognitive-Behavioral Therapy (CBT) and Depression

Kognitivno-bihevioralna terapija (KBT) i depresija

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ABSTRACT

Depressive disorder belongs to the group of affective disorders characterized by a depressed basic mood, the duration of which is at least two weeks. A combination of pharmacotherapy and psychotherapy methods is considered the most effective approach in the treatment of depression, with an emphasis on the importance of a good therapeutic alliance. Cognitive-behavioral therapy (CBT) is a key therapeutic option, focusing on modifying dysfunctional thoughts and behaviors. The paper describes a case of severe depressive disorder with dominant symptomatology of depressed basic mood, reduced energy, low self-esteem and emotional exhaustion. The treatment plan included the use of antidepressants and KB treatment.

Keywords: affective disorders, psychotherapeutic approach, combined therapy

SAŽETAK

Depresivni poremećaj pripada grupi afektivnih poremećaja karakteriziran sniženim osnovnim raspoloženjem, čije trajanje je najmanje dvije sedmice. Kombinacija farmakoterapije i psihoterapijskih metoda smatra se najučinkovitijim pristupom u liječenju depresije, s naglaskom na važnost dobre terapijske alijanse. Kognitivno-bihevioralna terapija (KBT) predstavlja ključnu terapijsku opciju, fokusirajući se na modificiranje disfunkcionalnih misli i ponašanja. U radu je opisan prikaz slučaja teškog depresivnog poremećaja uz dominirajuću simptomatologiju sniženog osnovnog raspoloženja, redukcije energije, niskog samopouzdanja i emocionalne iscrpljenosti. Terapijski plan je uključivao primjenu antidepresiva i KB tretman.

Ključne riječi: afektivni poremećaji, psihoterapijski pristup, kombinovana terapija

INTRODUCTION

Depressive disorder is an affective disorder characterized by a low mood lasting for at least two weeks, with no previous episodes of mania or hypomania. Affective disorders are among the most common psychiatric conditions encountered in practice. Affective symptoms often appear in various physical and psychological disorders (e.g., organic causes, alcoholism, other addictions, schizophrenia, personality disorders). According to studies, the lifetime prevalence of depression is estimated to range from 1% to 19%, with one in five women and one in ten men experiencing a major depressive episode during their lifetime. Recent estimates indicate that over 150 million people worldwide are receiving treatment for depression. Depression can occur at any age but is most common between the ages of 25 and 40. This period coincides with the highest work potential, and many people are rendered incapable of working due to depression. Depression is somewhat more common in women than in men, with two depressed women for every one man. Given its frequent under recognition and inadequate treatment, depression is now one of the leading causes of disability, with a tendency for increasing healthcare system burdens. It is predicted that by 2030, depression will be the most burdensome disease for healthcare and social systems (1,2).

According to the ICD-10 classification, depressive episodes are classified as follows: F32 (mild, moderate, severe without psychotic symptoms, and severe with psychotic symptoms).

Mild depressive disorder (F32.0): a wide range of mood, behaviour, and other symptoms which patients and others usually consider as being markedly different from their usual behaviour and personality. Patients report a low mood, lack of energy, and inability to enjoy things, along with poor sleep.

Moderate depressive disorder (F32.1): key characteristics include low mood, inability to enjoy, reduced energy, and pessimistic thoughts.

Severe depressive disorder (F32.2): as the depression intensifies, symptoms become more pronounced, including feelings of worthlessness, guilt, poor health, nihilism, and possibly delusions and hallucinations, leading to a diagnosis of severe depression with psychotic symptoms (F32.3).

In depression, neurons do not produce enough neurotransmi tters, preventing nerve messages from being transmitted. Neurotransmitters like norepinephrine and serotonin are critical in regulating mood and emotions. A reduced presence of these neurotransmitters in brain areas controlling mood can result in depression (3).

Each therapeutic approach has its biopsychosocial basis. Medications have psychological effects, just as psychotherapy has biological correlates. Numerous clinical studies have shown that a combination of pharmacotherapy and psychotherapy is the most effective approach. Research by the National Institute of Mental Health (USA) has highlighted the importance of a good therapeutic alliance for the success of depression treatment. It is particularly significant for depressed patients, as the combination of psychotherapy and pharmacotherapy reduces the chances of discontinuation of any treatment approach (4,5).

Cognitive-behavioural therapy (CBT) is an indicated therapeutic option for a wide range of mental health disorders. CBT for depression is a structured, specific, and problem-oriented psychological approach (6,7).

Beck's Cognitive Model of Depression suggests that experien ces lead people to form assumptions or schemas about themselves and the world, which they use to organize their perceptions and evaluate behaviours. While the ability to predict and make sense of one's experiences is essential for normal functioning, some assumptions are rigid and resistant to change, making them dysfunctional. These assumptions often relate to what people need to be happy and are often counterproductive (8,9).

Behavioural models of depression emphasize the reduction of rewarding behaviours, lack of self-rewarding, self-punishing behaviour, skills deficits, lack of assertiveness, poor problem-solving skills, exposure to aversive situations, sleep deprivation, and inconsistency between behaviour and consequences. Cognitive-behavioural interventions in treating depression include cognitive strategies for education, cognitive restructuring (identifying and modifying dysfunctional cognitions), and behavioural strategies for planning activities, self-rewarding, problem-solving training, and assertiveness and social skills training (10,11).

AIM

The aim of the paper was to present the role of cognitive-behavioural therapy in the treatment of depression.

CASE REPORT

We present a case of a 49-years-old (AM) patient, unemployed economic technician, married, with two grown children. She grew up in a supportive family environment and lost her father to a heart attack 10 years ago. She was employed for many years but lost her job three years ago due to her own mistake, after which she stopped seeking new employment. She has no social relations, communicates minimally with her children, and has formal communication with her household members. She does not leave the house and is not actively involved in household chores.

She is hypertensive and takes prescribed medication only when urged by her mother. For the last three years, she has been under psychiatric treatment for depression (diagnosis F32.2), currently on sertraline (50mg), quetiapine (25mg), and olanzapine (5mg). Previous pharmacotherapy options have not improved her condition.

Problem development history: after losing her job, the patient began seeing herself as incapable and prone to mistakes. She struggled with staying at home and lacked work-related activities. She avoided household tasks, spent most of her time alone in her room, and avoided contact with former colleagues. Her communication with her children was minimal as she felt ashamed of her mistakes. She felt distanced from her husband, perceiving him as viewing her as incompetent. She only felt secure with her mother and found understanding with her younger sister, who did not talk about her job but reminisced about their childhood.

Psychiatric status: the patient presents a neglected appearance, oriented in all directions, and independently mobile. She displays a slumped posture, a low mood, anxiety, emotional incontinence, and a slow thought process. She holds rigid, borderline delusional guilt-based thoughts, low self-esteem, and a negative view of her present, past, and future. She denies suicidal ideation and perceptual disturbances. Her volitional sphere is entirely restricted.

Case formulation

A longitudinal view on cognition and behaviour: before losing her job, the patient was diligent, perfectionistic, and took care of her appearance and health. Her parents, both educated and successful in their careers, had high expectations, especially her mother, who was recognized for being "perfect" in everything. Dysfunctional rules were identified: "Incompetent people make mistakes," "Do it perfectly or don't do it at all," "No one likes incompetent people - they are no good for their family or colleagues."

Treatment planning and course

In agreement with the patient, the dose of sertraline was increased to 100mg daily, and cognitive-behavioural therapy (CBT) was initiated.

At the start of treatment, education on depression was provided, emphasizing that depression is a medical condition for which she is not responsible, thereby reducing feelings of guilt. Short- and long-term goals were set, focusing on improving self-care, household participation, pleasant activities, social interactions, assertiveness, mood, and self-perception. Long-term goals included finding a job and traveling with family.

An initial Beck Depression Inventory (BDI) score of 49 and a Hamilton Depression Rating Scale score of 25 were recorded. Twelve sessions were planned, with weekly visits. A therapeutic diary was introduced to monitor situations that trigger negative emotions and thoughts. Self-monitoring revealed passive rumination, prompting behavioural activation to gradually resume daily activities. Some enjoyable activities like cooking and gardening were identified and planned to support both the patient and her family.

Cognitive interventions included identifying negative automatic thoughts and dysfunctional schemas. Cognitive restructuring replaced negative thoughts with realistic, functional alternatives. For example, "If I forget to buy something, I can go back to the store later," "I can express myself imperfectly without others judging me," "I am educated and capable."

The cognitive continuum technique was used to counter black-and-white thinking about self-worth, helping the patient recognize her position between the extremes of "perfect" and "incompetent." Relapse prevention: the patient was taught strategies to cope with future depressive episodes, including recognizing triggers and using the coping skills learned during therapy.

DISCUSSION

Over three months, twelve one-hour sessions were held weekly. The patient showed gradual improvement in behavioural, cognitive, and affective aspects. The patient became more active, communicated better with family, performed household chores, and improved her self-care and physical appearance. The BDI score decreased to 28, and the Hamilton Depression Scale score to 18. Following the therapy, regular follow-up visits continued for pharmacotherapy monitoring.

CONCLUSION

This case demonstrates the use of cognitive-behavioural therapy for severe depression, alongside pharmacotherapy (sertraline, olanzapine, and quetiapine). The patient expressed a desire for psychotherapy, as previous pharmacotherapy options had not helped. CBT focused on identifying and modifying unrealistic guilt and incompetence beliefs, which were key in the development and maintenance of her depression. Given that the patient was treated simultaneously with pharmacotherapy and psychotherapy, it is difficult to determine the exact contribution of each approach to the symptom improvement. However, the patient reported that identifying and modifying negative thoughts and accepting her mistakes, as well as having a good therapeutic alliance, were most helpful.

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Naziv i puna adresa institucije u kojoj je autor-koautor/i zaposlen/i (jednako za sve autore), na engleskom jeziku, te na kraju rada navedena adresa kontakt-autora.

Sažetak na našem jeziku, kao i na engleskom - max. 200–250 riječi, s najznačajnijim činjenicama i podatcima iz kojih se može dobiti uvid u kompletan rad.
Ključne riječi - Key words, na našem jeziku i na engleskom, ukupno do pet riječi, navode se ispod Sažetka, odnosno Abstracta.

SADRŽAJ

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

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

UVOD

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

MATERIJAL I METODE

Potrebno je da sadrži opis originalnih ili modifikaciju poznatih metoda. Ukoliko se radi o ranije opisanoj metodi dovoljno je dati reference u literaturi. U kliničko-epidemiološkim studijama opisuju se: uzorak, protokol i tip kliničkog istraživanja, mjesto i vrijeme istraživanja. Potrebno je opisati glavne karakteristike istraživanja (npr. randomizacija, dvostruko slijepi pokus, unakrsno testiranje, testiranje s placebom itd.), standardne vrijednosti za testove, vremenski odnos (prospektivna, retrospektivna studija), izbor i broj ispitanika – kriterije za uključivanje i isključivanje u istraživanje.

REZULTATI

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

DISKUSIJA

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

ZAKLJUČAK

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

LITERATURA - Upute za citiranje - pisanje literature

Literatura se obavezno citira po **Vankuverskim pravilima**.

Svaku tvrdnju, saznanje ili misao treba potvrditi referencom. Reference u tekstu treba označiti po redoslijedu unošenja arapskim brojevima u zagradi na kraju rečenice. Ukoliko se kasnije u tekstu pozivamo na istu referencu, navodimo broj koji je referenca dobila prilikom prvog unošenja/pominjanja u tekstu. Literatura se popisuje na kraju rada, rednim brojevima pod kojim su reference unesene u tekst (ulazni broj reference), a naslov časopisa se skraćuje po pravilima koje određuje Index Medicus. Ukoliko je citirani rad napisalo više autora, navodi se prvih šest i doda "et al.".

Vrlo je važno ispravno oblikovati reference prema uputama koje se mogu preuzeti na adresama National Library of Medicine Citing Medicine http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=citmed.TOC&depth=2 , ili International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

Sample References http://www.nlm.nih.gov/bsd/uniform_requirements.html.