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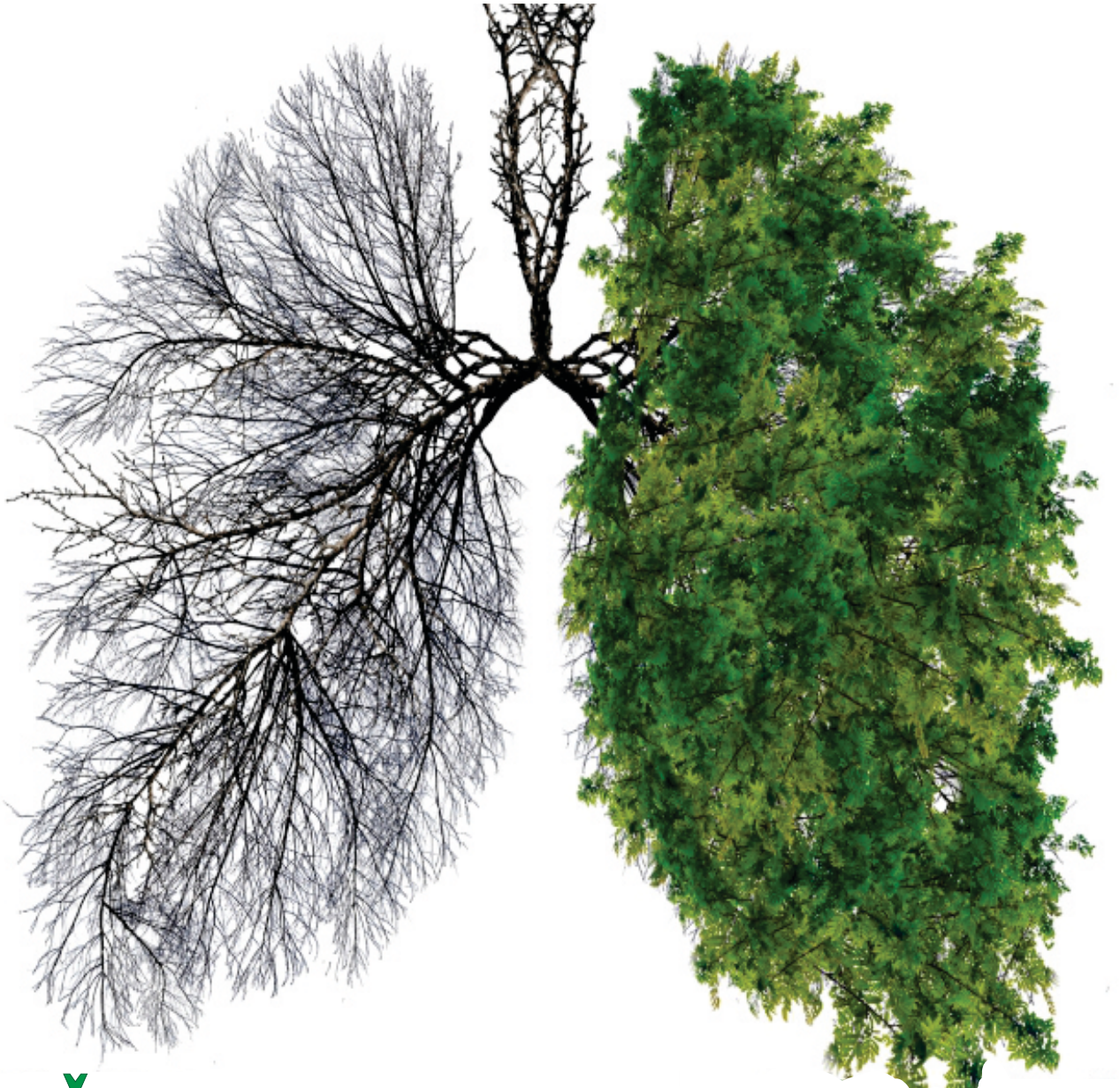

ČUVAJTE SVOJE ZDRAVLJE!

31. maj
Svjetski dan nepušenja

KLINIČKI CENTAR UNIVERZITETA SARAJEVO

Bosnia and Herzegovina was the fourth country in Europe that developed National version of HeartScore program !

Bosna i Hercegovina je bila četvrta zemlja u Evropi koja je razvila Nacionalnu verziju HeartScore programa !

Bosnia and Herzegovina version of HeartScore is developed on the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Serbian and Croatian! Program is easy to use and accessible at www.heartscore.org/eu !

Verzija za Bosnu i Hercegovinu razvijena je na jezicima naroda Bosne i Hercegovine, bosanskom, srpskom i hrvatskom! Program je jednostavan za upotrebu preko web stranice www.heartscore.org/eu !

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Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu
New Central Medical Building - Clinical Center University of Sarajevo

Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

CHA_2DS_2-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

Risk factor-based point-based scoring system - CHA_2DS_2 -VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

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

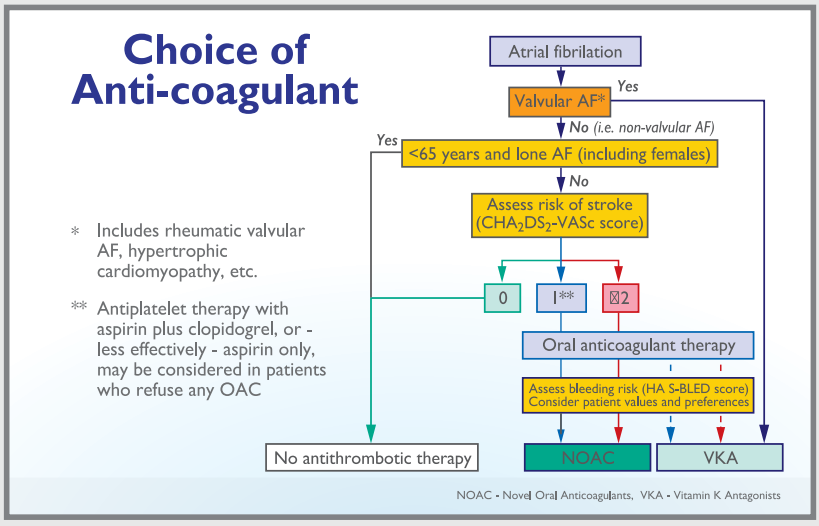
Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

Risk factors for stroke and thrombo-embolism in non-valvular AF

Major risk factors	Clinically relevant non-major risk factors
Previous stroke	CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ⊠ 40%]
TIA or systemic embolism	Hypertension
Age ⊠75 years	Diabetes mellitus
	Age 65-74 years
	Female sex
	Vascular disease

AF = atrial fibrilation; EF = ejection fraction (as documented by echocardiography, radio nudide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left venticular; TIA = trasient ischaemic attack.

Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!



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AIMS AND SCOPE

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Address:
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Clinical Center University of Sarajevo,
71000 Sarajevo,
Bolnička 25,
Bosnia and Herzegovina,
Phone: +387 33 298 514
Web. www.kcus.ba
Technical secretariat: svjetlana.barosevcic@kcus.ba

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Case Reports

Evaluation of Glasgow Aneurysm Score for ruptured abdominal aortic aneurysm repair, based on our experience at the Clinical Center University of Sarajevo

Evaluacija Glasgow Aneurysm Score kod pacijenata sa rupturom aneurizme abdominalne aorte - iskustva u Kliničkom Centru Univerziteta u Sarajevu

Amel Hadžimehmedagić*, Muhamed Djedović, Damir Kurtagić, Bedrudin Banjanović, Ilirijana Haxhibeqiri-Karabdić, Slavenka Štraus

Clinic of Cardiovascular Surgery, Clinical Center University of Sarajevo, Bolnička 25, 7 1000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: the mortality and morbidity rate due to abdominal aortic aneurysm rupture (RAAA) still remains high. In order to improve the final outcome surgical decision-making involves quickly evaluating. To enhance the objectivity and efficacy of surgical treatment, a prediction of RAAA outcomes is crucial. Several models have been developed to predict death after intervention in patients with an RAAA. Glasgow Aneurysm Score is one of the most commonly used models. Aim: to evaluate the accuracy of the most frequently used GAS system in predicting mortality and its practical use in clinical decision-making. Materials and methods: a retrospective, comparative cohort study was conducted in all 86 consecutive surgically treated patients with an RAAA in the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo in the four years period, from June 2019 to June 2023. Glasgow Aneurysm Score (GAS) was calculated and compared with final score. Results: the results show that total mortality rate was 23.3%, the mean GAS for the 86 patients who underwent surgery was 100.33 +/- 17.57. No statistically significant difference in GAS values was found between patients who died and patients who survived surgery and in the 30-day postoperative period. Conclusion: our research has shed light on the limitations of existing scoring systems, including the Glasgow Aneurysm Score system.

Keywords: abdominal aortic aneurysm, rupture, Glasgow Aneurysm Score

SAŽETAK

Uvod: stopa mortaliteta i morbiditeta zbog rupture aneurizme abdominalne aorte (RAAA) i dalje se održava na visokom nivou. Kako bi se rezultati poboljšali, donošenje hirurških odluka za pacijente sa rupturom aneurizme abdominalne aorte uključuje brzu evaluaciju. Da bi se poboljšala objektivnost i efikasnost hirurškog liječenja, predviđanje ishoda RAAA je ključno. Razvijeno je nekoliko modela za predviđanje postoperativne smrnosti kod pacijenata sa RAAA. Glasgow Aneurysm Score je jedan od najčešće korištenih modela. Cilj istraživanja: procijeniti tačnost najčešće korištenog GAS sistema u predviđanju mortaliteta i njegovu upotrebu u kliničkom donošenju odluka. Materijal i metod: retrospektivna, komparativna kohortna studija provedena je na svih 86 uzastopno liječenih kirurški pacijenata sa RAAA na Klinici za kardiovaskularnu hirurgiju Kliničkog centra Univerziteta u Sarajevo u periodu od četiri godine, od juna 2019. do juna 2023. godine. Izračunat je i upoređen Glasgow aneurysm Score (GAS) sa konačnim rezultatom. Rezultati: Rezultati pokazuju da je ukupni mortalitet u uzorku 23,3% srednji GAS za 86 pacijenata koji su podvrgnuti operaciji bio 100,33 +/- 17,57. Nije nađena statistički značajna razlika u vrijednostima GAS-a između umrlih pacijenata i pacijenata koji su preživjeli operaciju iu 30-dnevnom postoperativnom periodu. Zaključak: naše istraživanje je bacilo svjetlo na ograničenja postojećih sistema bodovanja, uključujući GAS skor sistem.

Ključne riječi: Aneurizma abdominalne aorte, ruptura, Glasgow aneurysm score

INTRODUCTION

The mortality for ruptured abdominal aortic aneurysm (RAAA) remains high in the face of medical progress. Approximately 5.6-17.5 per 100,000 person-years in Western countries, and the overall mortality rate of patients with an RAAA is circa 80% (1). In patients reaching the hospital and undergoing intervention the death rate ranges between 24% and 49% (2). Treatment options include endovascular aneurysm repair (EVAR) and open surgical repair (OSR). Predictors of survival, such as hemodynamic shock, loss of consciousness, sex, and aneurysm anatomy, are independent of the chosen treatment. The idea for the analysis that is the subject of this article was born during a comparative review of treatment outcomes in the earlier and new series of treated patients. Because of favorable treatment outcome trend was established, we came up with the idea of making a comparison of the actual outcome and the outcome that would be assessed based on the application of the GAS numerical score system. After the first dozen of analyses, we established that the predictive calculation through the GAS numerical system does not match the actual situation. For this reason, we searched for similar opinion in recent research reports in available databases. The conclusions were similar.

Not only do preoperative factors predict mortality in RAAA, but the postoperative condition might also have a clinical impact on survival. The context of surgical decision-making for patients with ruptured abdominal aortic aneurysms (RAAA) involves quickly evaluating factors like the patient's current condition, health history, and functional ability to determine if surgery is both appropriate and likely to result in survival. To enhance the objectivity and efficacy of surgical treatment, a prediction of RAAA outcomes is crucial. Several models have been developed to predict death after intervention in patients with an RAAA: the Glasgow Aneurysm Score (GAS), the Vancouver scoring system, the Edinburgh Ruptured Aneurysm Score (ERAS), and the Hardman index. The GAS and Hardman Index were established in the 1990s (3). Glasgow Aneurysm Score value above 78.5 is associated with almost threefold increase in mortality. Recent data reveals a troubling increase in RAAA cases over time, despite a doubling of elective repairs. For instance, one study reported an increase from 5.6 cases per 100,000 person-years in the period 1971-1986 period to 10.6 cases per 100,000 person-years in 2000-2004 (4,5,6). Given the complexity of RA, further scientific inquiry is necessary to improve the understanding and management of this condition.

AIM

The main objective of this study was to evaluate the accuracy of the most frequently used GAS system in predicting mortality and its practical use in clinical decision-making.

MATERIALS AND METHODS

This retrospective, comparative cohort study was conducted in all consecutive surgically treated patients with an RAAA in the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo in the four years period, from June 2019 to June 2023. The primary endpoint was the combined 30-day or in-hospital death rate. Glasgow Aneurysm Score was calculated with the formula: age (years) + 7 for cardiac comorbidity (defined as previous history of myocardial infarction, cardiac surgery, angina pectoris or arrhythmia) + 10 for cerebrovascular comorbidity (defined as previous history of stroke or transient ischemic attack) + 17 for shock (defined as hemorrhagic shock based on blood loss and hemodynamic stability) + 14 for renal insufficiency (defined as a preoperative serum creatinine >120 μmol/L). With regard to testing the accuracy of the score system, inclusion criteria included all operated patients with abdominal aortic aneurysm rupture, while exclusion factors were death during preoperative preparation or immediately during the surgical procedure. The remaining patients constituted the total sample (N=86).

Surgical Technique: all surgeries were performed under general endotracheal anesthesia by experienced vascular surgeons as an open repair-conventional median laparotomy approach.

Data collection: patient data, including preoperative characteristics, perioperative data, postoperative outcomes, and complications, were collected and entered into a Microsoft Excel database. Follow-up data were recorded for mortality, myocardial infarction, newly onset heart rhythm abnormalities, renal dysfunction, cerebrovascular incidents, and extremity ischemia. Based on the presented formula, the GAS score was calculated for each patient, and then the individual and overall outcome was determined. The obtained numerical value indicated an individual prediction that was compared with the realized postoperative outcome. Statistical analysis Statistics were calculated for the baseline demographic and clinical features, as well as treatment outcomes, using the IBM SPSS Statistics software (IBM Corp, Armonk, NY). Categorical variables were presented as numbers and percentages. A two-tailed probability value of $P < .05$ was considered significant.

RESULTS

All 86 patients with an RAAA underwent urgent repair of an RAAA at the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo. Early follow-up data, including 30-day mortality, at least 30 days postoperatively were complete. Infrarenal clamping was possible in all of the patients, while none of the patients required suprarenal clamping. Out of 86 patients, 74 were male, and 12 were female, with a median age of 71 +/- 7.404. 12 out of 86 patients had records of previous cerebrovascular comorbidities such as CVI or TIA, and 32 patients had a history of underlying or previous cardiac disease. The majority of patients, 74 of them, had renal insufficiency), and 60 patients were in shock. The patients' comorbidities included per the GAS are shown in the following tables (Tables 1,2,3,4).

Table 1 Number of Patients with Cerebrovascular comorbidities

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	74	86.0	86.0	86.0
	Yes	12	14.0	14.0	100.0
	Total	86	100.0	100.0	

Table 2 Number of Patients with Cardiac comorbidities

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	54	62.8	62.8	62.8
	Yes	32	37.2	37.2	100.0
	Total	86	100.0	100.0	

Table 3 Number of patients with Renal insufficiency

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	12	14.0	14.0	14.0
	Yes	74	86.0	86.0	100.0
	Total	86	100.0	100.0	

Table 4 Number of patients in preoperative shock

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	26	30.2	30.2	30.2
	Yes	60	69.8	69.8	100.0
	Total	86	100.0	100.0	

Table 5 Number of patients who had a lethal outcome.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	no	66	76.7	76.7	76.7
	yes	20	23.3	23.3	100.0
	Total	86	100.0	100.0	

The 30-day mortality in our cohort study was found to be 23.3%, as shown in Table 5.

In Formula for outcome and mortality risk GAS (age in years) + (17x shock) + (7x myocardial disease) + (10x cerebrovascular disease) + (14x renal disease), a score >95 indicates high mortality risk (>80%). Glasgow scores and their frequency in our cohort study is shown on Figure 1.

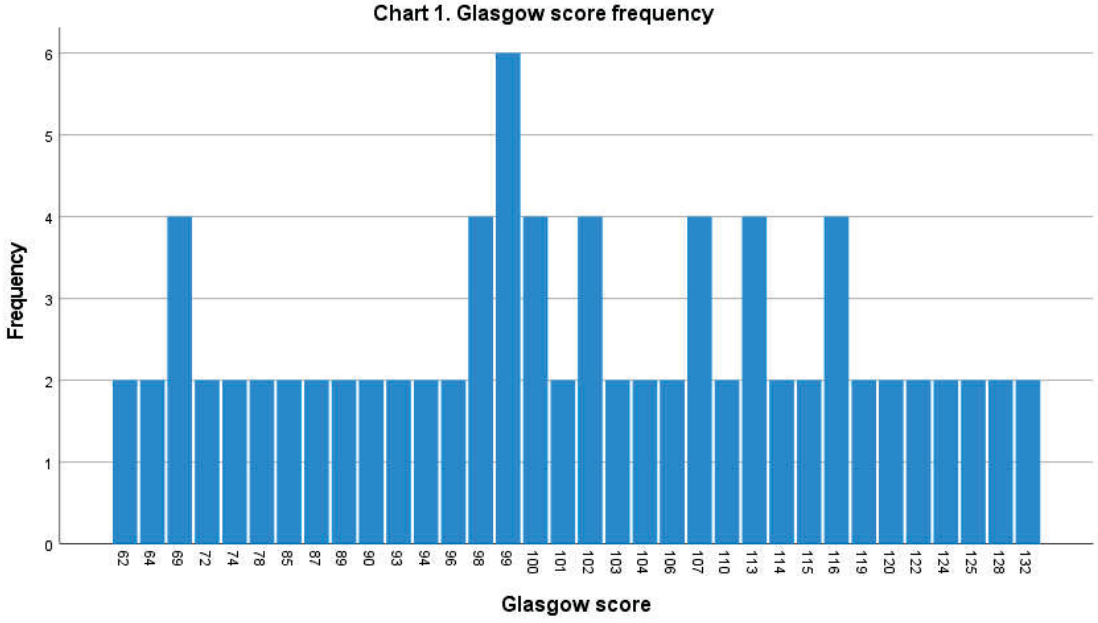

Figure 1 Glasgow score frequency.

Table 6 Glasgow scores summarized.

	N	Minimum	Maximum	Mean	Std. Deviation
Glasgow score	86	62	132	100.33	17.571
Valid N (listwise)	86				

The results show that the mean GAS for the 86 patients who underwent surgery was 100.33 +/- 17.57 (Table 6).

The statistical analysis showed that out of 86 patients in this study, males had a statistically significantly higher chance of lethal outcome (p= 0.04) than female patients. (Table 7, Figure 2)

Table 7 **Correlations between comorbidities, Glasgow score, and outcome.**

		Age	Cerebrovascular comorbidities	Cardiac comorbidities	Renal disease	Hemorrhagic shock	Glasgow score	Sex	Lethal outcome
Age	Pearson Correlation	1	.209	.024	.201	.357**	.669**	.073	.005
	Sig. (2-tailed)		.053	.830	.064	.001	.000	.506	.966
	N	86	86	86	86	86	86	86	86
Cerebrovascular comorbidities	Pearson Correlation	.209	1	.384**	.162	.119	.461**	.032	-.063
	Sig. (2-tailed)	.053		.000	.136	.275	.000	.773	.566
	N	86	86	86	86	86	86	86	86
Cardiac comorbidities	Pearson Correlation	.024	.384**	1	.310**	.192	.454**	-.171	.260*
	Sig. (2-tailed)	.830	.000		.004	.076	.000	.115	.016
	N	86	86	86	86	86	86	86	86
Renal insufficiency	Pearson Correlation	.201	.162	.310**	1	.612**	.738**	-.032	.222*
	Sig. (2-tailed)	.064	.136	.004		.000	.000	.773	.040
	N	86	86	86	86	86	86	86	86
Hemorrhagic shock	Pearson Correlation	.357**	.119	.192	.612**	1	.786**	.119	.243*
	Sig. (2-tailed)	.001	.275	.076	.000		.000	.275	.024
	N	86	86	86	86	86	86	86	86
Glasgow score	Pearson Correlation	.669**	.461**	.454**	.738**	.786**	1	.050	.201
	Sig. (2-tailed)	.000	.000	.000	.000	.000		.647	.064
	N	86	86	86	86	86	86	86	86
Sex	Pearson Correlation	.073	.032	-.171	-.032	.119	.050	1	-.222*
	Sig. (2-tailed)	.506	.773	.115	.773	.275	.647		.040
	N	86	86	86	86	86	86	86	86
Lethal outcome	Pearson Correlation	.005	-.063	.260*	.222*	.243*	.201	-.222*	1
	Sig. (2-tailed)	.966	.566	.016	.040	.024	.064	.040	
	N	86	86	86	86	86	86	86	86

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

The patients who underwent aortic rupture surgery and had a history of previous cardiac disease were found to have had a statistically significant higher chance of lethal outcome than patients with no cardiovascular disease p=0.016. (Table 7, Figure 2).

The patients who had previous renal disease, which was the majority of them, also showed a higher chance of mortality (p=0.04), and patients who showed signs of shock (primarily hemorrhagic) as well (p=0.024). (Table 7, Figure 2).

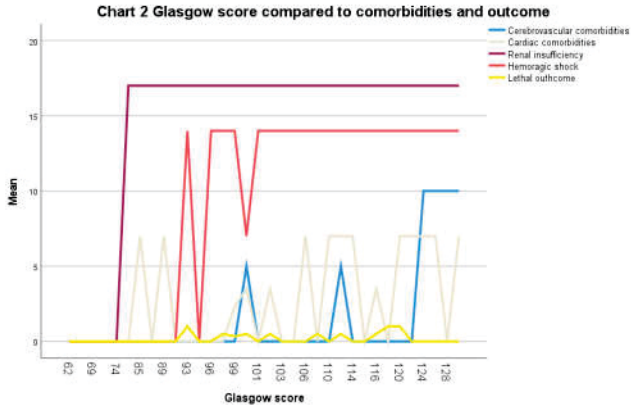

Figure 2 **Glasgow score compared to comorbidities and outcome.**

When observing the Glasgow scores, we can conclude that it was significantly higher in patients of older age, patients with cardiac, cerebrovascular, and renal disease, and patients in shock (as shown in Table 7). This was expected, considering that GAS is based on evaluating the presence of mentioned comorbidities.

With regard to the correlation between GAS and lethal outcome, no statistically significant difference in GAS values was found between patients who died and patients who survived surgery and in the 30-day postoperative period (p= 0.064). (Table 7. And Chart 2.)

DISCUSSION

The management of a ruptured abdominal aortic aneurysm (RAAA) continues to be a formidable challenge in the field of vascular surgery due to its high mortality rates, even in the era of advanced medical care and surgical techniques. This study aimed to evaluate the accuracy and practical utility of the Glasgow Aneurysm Score (GAS) in predicting mortality among patients who underwent surgical repair for RAAA. The study found a 30-day mortality rate of 23.3% among the 86 patients who underwent surgical intervention for RAAA. This rate is in line with previous reports in the literature, highlighting the gravity of this condition and the urgent need for improved risk prediction and management strategies (7,8). The analysis revealed that significant predictors of mortality among RAAA patients that are included in GAS are correlated with higher mortality rates. Patients with a history of cardiac disease, cerebrovascular disease, renal disease, and those presenting with shock were more likely to experience a poor outcome following open surgical repair. Our findings shed light on critical factors that influence outcomes in RAAA cases and can guide clinical decision-making.

One of the notable demographic aspects of our patient cohort was the predominance of male patients, with a male-to-female ratio of approximately 6:1. This skewed gender distribution is consistent with previous literature on aortic aneurysms, suggesting a higher incidence of aneurysmal disease in men. Intriguingly, our study revealed that males had a statistically significantly higher chance of lethal outcomes (p=0.04) than their female counterparts, which is different than in other studies that we have found (9). This gender-based discrepancy in RAAA outcomes merits further investigation.

The influence of age on RAAA outcomes is a well-documented aspect of aneurysm management. In our study, we found that GAS was significantly higher in older patients, aligning with the established understanding that advanced age is a significant risk factor for adverse outcomes in aortic aneurysm repair. This underscores the importance of considering age in the risk assessment process for RAAA patients.

Comorbidities play a pivotal role in determining the prognosis of patients undergoing RAAA repair. Patients with a history of cardiac disease were found to have a statistically significant higher chance of lethal outcomes (p=0.016) in our study. This highlights the critical need for meticulous preoperative cardiac evaluation and optimization to mitigate the heightened risk associated with cardiovascular comorbidities.

Renal insufficiency was a prevalent comorbidity in our patient cohort, affecting the majority of individuals. Our findings indicate that patients with previous renal disease had a higher chance of mortality (p=0.04). Given the substantial renal complications associated with RAAA repair, including acute kidney injury, our results underscore the importance of proactive renal assessment and management in this population.

The presence of shock, primarily of hemorrhagic origin, was a common clinical presentation in our study, affecting 60 out of the 86 patients. Shock is a critical factor in RAAA cases, often indicative of severe hemodynamic instability. Our findings revealed that patients in shock had a statistically significant higher chance of mortality. This highlights the critical importance of prompt recognition and resuscitation efforts to stabilize hemodynamics in RAAA patients.

The GAS, a composite score that takes into account age and the presence of comorbidities, is a valuable tool for risk stratification in aortic aneurysm repair. However, our analysis found no statistically significant difference in GAS values between patients who survived and those who did not within the 30-day postoperative period (p= 0.064). This result challenges the utility of GAS as a reliable predictive tool for RAAA mortality in the contemporary patient population. While GAS serves as a valuable predictor of overall risk, it may not be a direct indicator of immediate postoperative outcomes in RAAA cases.

These findings emphasize the importance of considering individual patient characteristics beyond the GAS score when assessing the prognosis of RAAA cases. The GAS system had previously shown promise in predicting outcomes for elective AAA repair (10,11). Its performance appears to deteriorate when applied solely to RAAA patients, as seen in the present study. Few other studies showed the same results as the one published by Tambyraja A, et al. in 2005, and that is that the GAS system and Hardman index were poor predictors of postoperative mortality after repair of a ruptured AAA. The same findings were noted in the research by van Beek CS, et al, which included 449 patients, and

another study by Cornelis C, et al. in 2016 in which they evaluated five different scoring systems, and found that none of the evaluated scores allows a prediction accurate enough to identify patients who should not undergo operations for their RAAA (12). This finding aligns with the notion that RAAA cases are inherently more complex and unpredictable, making it challenging to rely on preoperative variables alone for outcome prediction. Although different types of numeric score systems for outcome prediction exists, it seems that most of them are too much complex to be practical. GAS system is the simplest and mostly used because of that. However, some sytems are outdated and no longer able to predict outcomes accurately in the era of modern surgical technique. More recent reports openly criticize existing predictive systems because of its relatively low positive predictive value for death and major morbidity (13). Moreover, they labeled them as poor predictors of postoperative mortality after repair of a ruptured AAA (14).

The idea of creating more accurate prediction systems is almost ten years old, so some studies have already been published that promote a different approach in assessing the final outcome (15,16). For instance, there are some offers such as internal validation systems or system invented by Vascular Study Group of New England which is applicable not only for vascular emergences, but for cardiac and trauma patients either (17,18). Furthermore, according to current reports, the first analyzes and prognostic calculations using artificial intelligence have appeared so we can expect a generally accepted uniform predictive system (19,20).

CONCLUSION

In conclusion, our research has shed light on the challenges of predicting mortality in patients with ruptured abdominal aortic aneurysm (RAAA) and the limitations of existing scoring systems, including the Glasgow Aneurysm Score (GAS). The decision to provide or withhold intervention in RAAA cases is complex and critical, and our study underscores the need for highly accurate prediction models to guide such decisions. Despite the extensive evaluation, in our research, the GAS did not meet the threshold for reliable clinical decision-making in this context. Therefore, our findings suggest that the GAS system, along with other existing scoring models, requires further evaluation and refinement. Future research efforts should focus on improving the accuracy of these models to better assess the chances of successful intervention in RAAA cases. Until then, while these models may be useful for comparing case mixes between hospitals and providing tailored prognoses, they should be employed with caution in guiding the decision about intervention in individual patients.

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Reprint requests and correspondence:
Amel Hadžimehmedagić, MD, PhD
Clinic of Cardiovascular Surgery
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: amelskih@gmail.com
ORCID ID: 0000-0001-9274-6114

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The importance of D-dimer values evaluation in the detection of pulmonary embolism

Važnost procjene vrijednosti D-dimera u detekciji plućne embolije

Spomenka Kristić[1*], Amela Begić[2], Sandra Vegar-Zubović[1], Amila Bašić[2]

[1]Clinic of Radiology, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[2]Clinic of Nuclear Medicine and Endocrinology, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: Pulmonary Embolism (PE) represents a life-threatening medical emergency that, given the serious complications, requires urgent application of anticoagulant therapy. The two imaging modalities most commonly used to diagnose PE are multislice computed tomography (MSCT) and ventilation/perfusion single-photon emission computed tomography (V/P SPECT). D-dimer is an intermediate product of degradation of fibrin molecules and its values in the plasma are increased in the case of PE, but also in other diseases. Aim: to determine whether there is a difference in D-dimer values in subjects with confirmed and excluded PE. Materials and methods: the study included 100 subjects with diagnosed PE by using MSCT and/or V/P SPECT and with measured values of D-dimer. Results: out of 100 subjects, PE was not diagnosed in 37 subjects, while 63 subjects PE was diagnosed. All subjects were divided into 2 groups: a group of subjects with confirmed PE and a group of subjects with excluded PE by using imaging methods. Average D-dimer values were calculated for both groups. Statistical analysis showed that there was no significant difference in D-dimer values between subjects with confirmed and excluded PE. Conclusion: D-dimer shows high sensitivity but low specificity in the detection of PE and it cannot be used as an independent parameter for diagnosing PE.

Keywords: pulmonary embolism, D-dimer, MSCT, V/P SPECT

SAŽETAK

Uvod: plućna embolija (PE) predstavlja po život opasno urgentno stanje koje obzirom na ozbiljne komplikacije zahtijeva što hitniju primjenu antikoagulantne terapije. Dvije slikovne metode koje se najčešće koriste za dijagnosticiranje PE su višeslojna kompjuterizirana tomografija (MSCT) i ventilaciono/perfuziona jednofotonska emisiona kompjuterizirana tomografija (V/P SPECT). D-dimer predstavljaju međuprodukt degradacije molekula fibrina i njegove vrijednosti u plazmi su povišene u slučaju PE, ali i kod drugih oboljenja. Cilj: utvrditi da li postoji razlika u vrijednostima D-dimera kod ispitanika sa potvrđenom i isključenom PE. Materijali i metode: u studiju je uključeno 100 pacijenata kod kojih je postavljena dijagnoza PE korištenjem MSCT i/ili V/P SPECT-a i kojima je urađen nalaz D-dimera. Rezultati: od ukupnog broja ispitanika kod njih 37 nije dijagnosticirana PE, dok je kod 63 ispitanika dijagnosticirana PE. Svi pacijenti su podijeljeni u 2 skupine: skupina pacijenata kod kojih je potvrđena PE i skupina pacijenata kod kojih je isključena PE imaging metodama. Za obje skupine su izračunate prosječne vrijednosti D-dimera. Statistička analiza je pokazala da ne postoji značajna razlika u vrijednostima D-dimera između pacijenata sa potvrđenom i isključenom PE. Zaključak: D-dimer pokazuje visoku senzitivnost ali nisku specifičnost u detekciji PE i kao takav ne može se koristiti kao samostalni parametar za dijagnosticiranje PE.

Ključne riječi: plućna embolija, D-dimer, CT, V/P SPECT

INTRODUCTION

Pulmonary embolism (PE) is a life-threatening medical emergency where the main pulmonary arteries and/or their branches are obstructed by thrombotic masses, which leads to compromised blood flow. Considering the serious complications of this disease, it is necessary to prescribe therapy as soon as possible. In most cases the terapy of choice is anticoagulant therapy, which in itself is associated with numerous risks (1,2).

Unfortunately, the clinical presentation together with anamnestic data and standard laboratory findings can arouse suspicion of the existence of PE, but they do not have sufficient sensitivity and specificity in diagnosing pulmonary embolism necessary for the application of anticoagulant therapy (2,3,4,5).

The two imaging methods with the highest sensitivity and specificity, most commonly used in diagnosing PE and monitoring the effects of prescribed anticoagulant therapy, are Multislice Computed Tomography (MSCT) and Ventilation/Perfusion Single-Photon Emission Computed Tomography (V/P SPECT) (1).

Both MSCT and V/P SPECT have their advantages, but both methods have a common disadvantage, the use ionizing radiation which is harmful, especially in younger people and women. Due to

the harmful effect of the mentioned imaging methods on health, it is necessary to correctly select subjects who will be subjected to either of the mentioned imaging methods.

In subjects with clinical suspicion of PE, first step in the evaluation is measuring the level of D-dimer in the blood, as this value is used to select subjects who will be referred for further imaging methods.

D-dimer is an intermediate product of the degradation of fibrin molecules and its values in the plasma are increased in the case of acute thrombosis due to the simultaneous activation of the coagulation and fibrinolysis processes. The detection of D-dimer in serum is performed through the detection of D-dimer antigen by using tests that bind anitibodies to epitopes present on D-dimer molecules and are not present on other intermediate products of fibrin degradation (6).

The negative predictive value of D-dimer is high and normal values of D-dimer in the blood indicate a low probability of PE, i.e. in the case of a normal D-dimer finding, we can practically exclude the existence of PE.

On the other hand, fibrin formation is not only increased in PE but also in various other conditions such as deep venous trombosis, disseminated intravascular coagulation (DIC), acute aortic dissection, aortic aneurysm, peripheral arterial disease, coronary artery disease, acute myocardial infarction, stroke, malignant diseases, inflammation, bleeding, trauma, surgical procedures and necrosis. Elevated D-dimer values in the serum are often registered in these pathological conditions as well (6,7). In other words, the positive predictive value of D-dimer is low and elevated D-dimer values are not sufficient to establish a diagnosis of PE.

AIM

The aim of this study was to determine whether there is a difference in D-dimer values in subjects with confirmed and excluded PE.

MATERIALS AND METHODS

The prospective study conducted at the Clinical Center University of Sarajevo included 100 consecutive adult subjects with preserved renal function in whom the competent clinician suspected the presence of PE and who underwent to D-dimer, MSCT and/or V/P SPECT examination within 48 hours.

The study did not include minors, pregnant women and subjects with impaired renal function (creatinine clearance <60 ml/min).

The subjects with clinically suspected PE and elevated D-dimer values were referred for MSCT and/or V/P SPECT examination of the thoracic organs. MSCT and/or V/P SPECT examination were performed only in subjects with pathological D-dimer values, considering that the negative predictive value of D-dimer is high and normal D-dimer values in the blood indicate a low probability of PE, i.e. in the case of a normal D-dimer values it is practically possible to rule out PE.

All MSCT examinations were performed on a machine with 64 or more rows of detectors. After obtaining the topogram and determining the scanning field that covers the area of the thoracic organs from the tops to the bases of the lungs, a contrast series of scans commenced. Iodine-based contrast agent was applied with an automatic syringe in the amount of 80 to 100 ml, depending on the subject's body weight, at a rate of 4 mL/S. The following parameters were used for scanning: SMART PREP technique, breath-hold scanning in layers of 0.5 mm (120 kV, 250 mA, gantry rotation time 0.75 s). If, during the analysis of the scans, the existence of a partial or complete defect in the contrast filling in the pulmonary arteries and their branches was determined, the examination was classified as positive for PE (8).

V/P SPECT examinations were performed according to a one-day standardized protocol recommended by the European Association of Nuclear Medicine (5). As the first part of the examination, ventilation tomography was performed with previous inhalation of Technegas. Immediately after the completed ventilation tomography, perfusion tomography was performed, after the application of Tc-99m-MAA. Acquisition - Ventilation: 30-50 MBq of Technegas; Acquisition - Perfusion: 100-120MBq 99mTc MAA. A wide-field gamma camera with a low-energy, high-resolution collimator with the following parameters was used for acquisition: matrix size 64 x 64, 128 projections/360°; duration: 10 sec/frame-V; 5sec/frame P. The analysis of V/P SPECT findings was performed according to the interpretation criteria of the European Association of Nuclear Medicine [5]. The examination was classified as positive for PE if at least one segmental perfusion defect or two subsegmental perfusion defects were observed, while at the same time ventilation was preserved in the same region/regions - "mismatch".

Subjects with PE confirmed by at least one of the imaging methods (MSCT and V/P SPECT) were classified as positive for the presence of PE.

D-dimer values were measured on a Siemens BCSXP device (Siemens Healthneers) using the Innovance D-dimer calibrator CA-600 System. D-dimer values higher than 0.55 (mg/L) were considered pathological (reference interval: 0.00 – 0.55 mg/L).

For statistical analysis of the results the Microsoft Excel 365 (Microsoft Corporation, Redmond, Washington, USA) and IBM SPSS ver. 26.0 (IBM, Armonk, New York, USA) software was used. The significance level $\alpha = 0.05$ was chosen, and p values lower than this were considered statistically significant.

The results consisted partly of nominal variables and partly of ordinal variables. However, most of the collected data belong to the group of continuous variables. The median ($\tilde{x}$) was used as a measure of their central tendency, and the interquartile range (ΔQ) was used as a measure of dispersion, given that the distribution does not follow a normal distribution.

The Mann-Whitney U test was used to compare groups of independent data that do not follow a normal distribution.

RESULTS

A total of 100 clinically suspected PE subjects based on pathological values of D-dimer who undergone to MSCT and V/P SPECT imaging studies were included in the study.

Out of the total number of subjects, 45 were male and 55 were female. The number of male subjects did not differ significantly from the number of female subjects (binomial test, $p = 0.368$).

The median age of the subjects was 60 years ($\Delta Q = 26$), with no significant differences between men and women (Mann-Whitney U test, $p = 0.521$).

Of the total number of subjects included in the study ($n = 100$), 37 of them were not diagnosed with PE, while 63 subjects

were diagnosed with PE and underwent anticoagulant treatment (Figure 1).

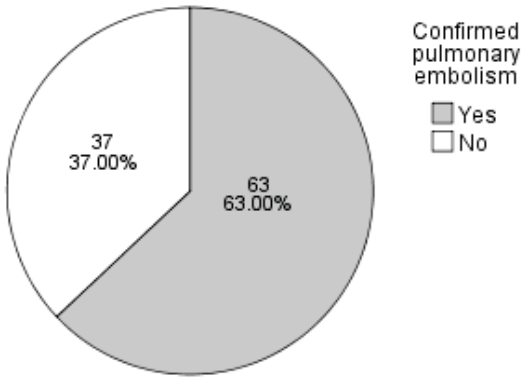

Figure 1 **The percentage of subjects with excluded and confirmed pulmonary embolism.**

All subjects were divided into 2 groups: a group of subjects with confirmed PE and a group of subjects with excluded PE, based on the finding of imaging methods. Average D-dimer values were calculated for both groups.

Table 1 **Median ($\tilde{x}$) and interquartile range (ΔQ) of D-dimer values for subjects with confirmed and excluded pulmonary embolism**.

	Confirmed pulmonary embolism			
	Yes		No	
	$\tilde{X}$	ΔQ	$\tilde{x}$	ΔQ
D-dimer	9.9	27.9	9.2	20.2

Subsequent analysis of D-dimer values in the participants included in the study revealed that there is no significant difference in D-dimer values between subjects with confirmed and excluded pulmonary embolism (Mann-Whitney U test, $p = 0.830$).

DISCUSSION

All subjects included in our study had elevated D-dimer values. One of the basic clinical criteria for suspecting PE and inclusion in the study, in addition to symptomatology, was elevated D-dimer values. The sensitivity of D dimer for diagnosing PE is 96.4%, while the negative predictive value is 99.6% (9,10,11), i.e. normal D-dimer values practically exclude the possibility of PE.

Based on subsequent analysis of D-dimer values in subjects included in the study, we observed that there is no significant difference in D-dimer values between subjects with confirmed and excluded pulmonary embolism. This result is in accordance with the literature that indicates the low specificity of D-dimer in the detection of PE, i.e. the sensitivity is only 40-50% depending on the laboratory test used (12). In other words, a positive finding of D-dimer does not automatically mean the presence of PE, given that D-dimer can be elevated in numerous other conditions such as liver disease, coronary artery disease and other cardiovascular diseases, malignant diseases, trauma, pregnancy, infections, inflammatory diseases, kidney diseases, recent surgical interventions and in elderly people (13).

A significant number of recent studies indicate the need to increase the cut-off value of D-dimer for diagnosing PE compared to those currently used in order to increase the specificity and positive predictive value of D-dimer in diagnosing PE [95,96], especially in elderly and oncological subjects.

CONCLUSION

All subjects included in our study had elevated D-dimer values, but subsequent analysis of D-dimer values showed that there was no significant difference in D-dimer values between subjects with confirmed and excluded pulmonary embolism. D-dimer shows high sensitivity but low specificity in the detection of PE and this test cannot be used as an independent parameter for diagnosing PE.

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Reprint requests and correspondence:
Kristić Spomenka, MD
Clinic of Radiology
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
E-mail: kristic.spomenka@gmail.com
ORCID ID: 000-002-3380-2339

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

One-year efficacy of first-line immunomodulatory therapy with glatiramer acetate measured by functional tests and MRI activity

Jednogodišnja učinkovitost prve linije imunomodulatorne terapije glatirameracetatom mjerena funkcionalnim testovima i aktivnosti na MRI

Admir Mehičević[1*], Emin Širbegović[2], Lejla Burnazović-Ristić[3], Enra Mehmedika-Suljić[1]

[1]Clinic of Neurology, Clinical Centre University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[2]General Hospital Tešanj, Braće Pobrić 17, 74260 Tešanj, Bosnia and Herzegovina
[3]Faculty of Medicine, University of Sarajevo, Čekaluša 90, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: multiple sclerosis (MS) is a chronic, autoimmune disease of the central nervous system. For diagnosis and for evaluation we use functional tests and magnetic resonance imaging of the brain. MS is a growing public health problem, so it is necessary to determine which disease-modifying therapy is appropriate to reduce disease activity and progression. Aim: to show whether there was efficacy of the first-line immunomodulator glatirameracetate in suppressing the activity and progression of the disease, measuring it with functional tests EDSS, 25-Foot Walking test, 9-Hole Peg test and disease activity on the brain magnetic resonance. Materials and methods: the research included 40 randomly selected patients with relapsing-remitting MS from the Clinic of Neurology, Clinical Center University of Sarajevo. In the course of the therapy, the three mentioned functional tests and a magnetic resonance imaging of the brain were performed at the beginning of the observation period and one year later. Results: out of 40 patients, 28 (70%) were female. Out of the total sample of 40 patients, 45% (n=18) belonged to the age group of 20-30 (n=15), and 37.5% to the age group of 30-40 years. There was no statistically significant difference in all three functional tests at the beginning and after one year follow-up ($p>0.05$). There was no statistically significant difference in activity and progression on magnetic resonance imaging of the brain after one year ($p>0.05$). There was a moderately strong to strong correlation between EDSS and T25FWT scales, as well as between EDSS and 9-HPT scales both at the beginning and at the end of the observation period. Conclusion: the results of this research clearly confirmed, with functional tests and MRI findings, the previously proven good effectiveness of glatiramer acetate in the treatment of multiple sclerosis.

Keywords: disease-modifying therapy, EDSS, T25FWT, 9-HPT, brain MRI

SAŽETAK

Uvod: multipla skleroza (MS) predstavlja hroničnu, autoimunu bolest centralnog nervnog sistema za čiju dijagnozu se koriste funkcionalni testovi i magnetna rezonanca mozga. MS predstavlja sve veći javnozdravstveni problem, s toga je potrebno odrediti koja imunomodulatorna terapija je odgovarajuća za smanjenje aktivnosti i progresije bolesti. Cilj: pokazati da li postoji efikasnosti prve linije imunomodulatora glatirameracetata u suzbijanju aktivnosti i progresije bolesti a istu mjerimo funkcionalnim testovima EDSS, 25-Foot Walking test, 9-Hole Peg test i aktivnost bolesti na magnetnoj rezonanci mozga. Materijali i metode: istraživanje je obuhvatilo 40 randomizirano odabranih pacijenata sa relapsno-remitirajućom MS sa Klinike za neurologiju, Kliničkog centra Univerziteta u Sarajevu. U toku terapije izvršeno je testiranje tri navedena funkcionalna testa i snimak magnetne rezonance mozga na početku perioda posmatranja i godinu dana nakon toga. Rezultati: od 40 pacijenata, 28 (70%) pacijenata je ženskog spola. Od ukupnog uzorka od 40 pacijenata, njih 45% (n=18) pripada dobnoj skupini 20-30 (n=15) godina, a 37,5% dobnoj skupini 30-40 godina. Ne postoji statistički značajna razlika u sva tri funkcionalna testa na početku i nakon godinu dana praćenja ($p>0.05$). Nema statistički značajne razlike u aktivnosti i progresiji na magnetnoj rezonanci mozga nakon godinu dana ($p>0.05$). Postoji umjereno jaka do jaka korelacija između EDSS i T25FWT skala, kao i između EDSS i 9-HPT skala kako na početku, tako i na kraju perioda posmatranja. Zaključak: rezultati ovog istraživanja jasno su potvrdili, funkcionalnim testovima i nalazima MRI-a, prethodno dokazanu dobru učinkovitost glatiramer acetata u liječenju multiple skleroze.

Ključne riječi: imunomodulatorna terapija, EDSS, T25FWT, 9-HPT, magnetna rezonanca mozga

INTRODUCTION

Multiple sclerosis is a severe neurological disease that mainly affects young population. The progression of clinical picture leads to a wide range of symptoms: from mild such as paresthesias up to severe disabilities and dependence on the support of another person. Functional tests along with disease activity and progression monitoring using brain magnetic resonance represent the basis for disease evaluation and choice of therapy. One of the functional tests that is used on a daily basis is the Expanded Disability Status Scale-EDSS that monitors the function of 9 functional systems of the central nervous system (1-4) Considering imaging methods, brain magnetic resonance represents the golden standard for diagnosis and evaluation of multiple sclerosis (5,6). Postcontrast opacification, as well as an increase in the number of lesions, speaks in favor of disease activity and/or disease progression (7,8). It has been proven that therapy with disease modifying drugs reduces the number of relapses and maintains remission (9,10). Drugs with a better safety profile such as glatiramer-acetate or interferons are most often used in the treatment of patients with a mild course of the disease (11,12).

AIM

The aim of this research was to determine whether functional tests are equally effective and sensitive in monitoring the progression of the disease in comparison with MRI in patients treated with glatiramer acetate.

MATERIALS AND METHODS

The research included 40 patients diagnosed with RRMS, treated at the Clinic of Neurology of the Clinical Center University of Sarajevo during 2022. The diagnosis of MS was established according to Mc Donald's diagnostic criteria. Anamnestic and diagnostic data, EDSS score and brain magnetic resonance findings were collected during the treatment and one year later. In the research we included patients over 18 years diagnosed with relapsing-remitting multiple sclerosis (RRMS) according to McDonald's criteria, treated with glatiramer-acetate over a year and with MRI at the beginning and one year later. We preformed functional tests (Expanded Disability Status ScaleEDSS, Timed 25-Foot Walking Test-T25FWT and 9-Hole Peg Test-9-HPT) at the beginning of the follow-up period and after one year. Exclusion criteria were patients with secondary progressive and primary progressive form of the disease and patients treated with other immunomodulating therapies.

RESULTS

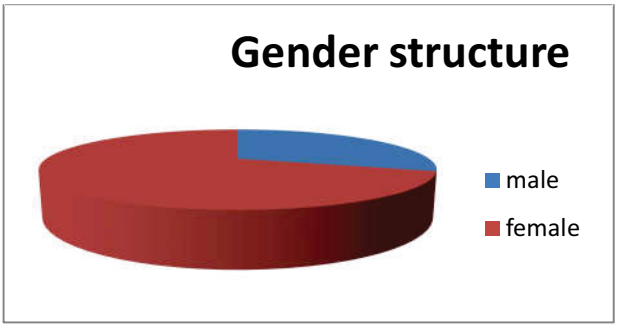

Figure 1 **Gender structure of patients.**

By analyzing the gender structure, we found that 70% (n=28) of patients treated with glatiramer-acetate were female, and 30% were male patients.

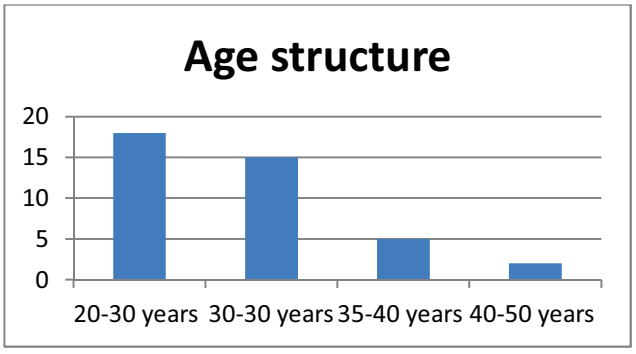

Figure 2 **Age structure of patients.**

Out of the total sample of 40 patients, 45% of them (n=18) belong to the age group of 20-30 (n=15) years, and 37,5% age group 30-40 years. Arithmetic mean of the age of patients treated with glatiramer-acetate was 25.3±7.109,

Table 1 **Descriptive statistics of functional tests at the beginning of the observation period and after a year.**

	At the beginning After a year	
	Glatirameracetat	Glatirameracetat
EDSS	2.125±0.9442	2.475±1.342
T25FWT (	7.55 (7.1-8.3)	7.5 (7.3-8.5)
9-HPT (s)	15.875±1.538	14.325±1.794

Statistical analysis proved that there was no statistically significant difference in the mean values of the EDSS scale after one year in patients on glatiramer-acetate therapy (Z=-1.182; p=0.07; p>0.05).

Table 2 **Representation of activity and progression on brain MRI in patients treated with glatiramer acetate.**

	Glatiramer-acetat	
	n	%
No activity and no progression	15	75
With activity, without progression	2	10
With progression, without activity	2	10
With progression and activity	1	5
Σ=	20	100
	Fisher Exact test: p=0.138	
n – Total number of participants		

Statistical analysis showed that there was no statistically significant difference in the activity and progression on magnetic resonance imaging of the brain after one year (p=0.138).

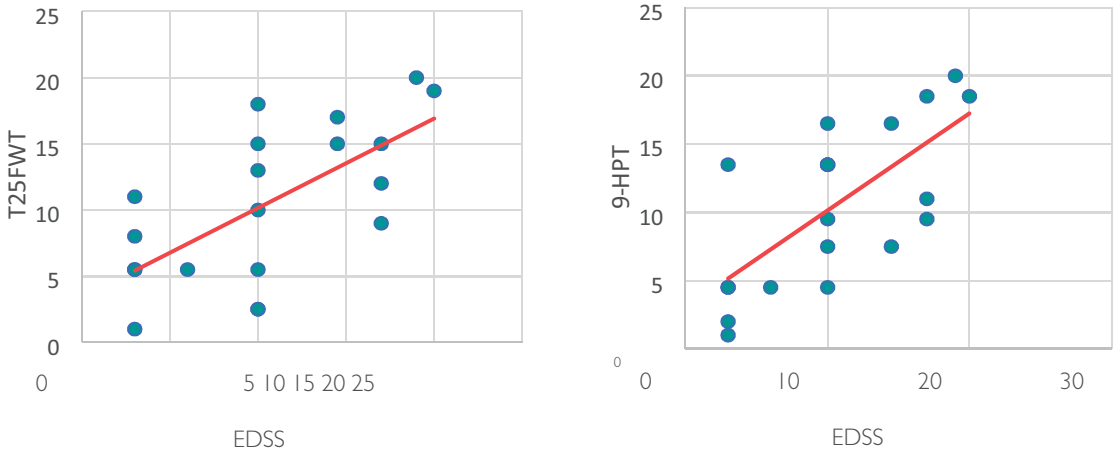

Figure 3 **Correlation of EDSS-T25FWT (left) and EDSS-9-HPT (right) at the beginning of the study in patients on glatiramer-acetate therapy.**

There was a strong correlation between EDSS and T25FWT (rs=0.659), and EDSS and 9-HPT (rs=0.696), at the beginning of the follow-up period in patients on glatiramer-acetate therapy.

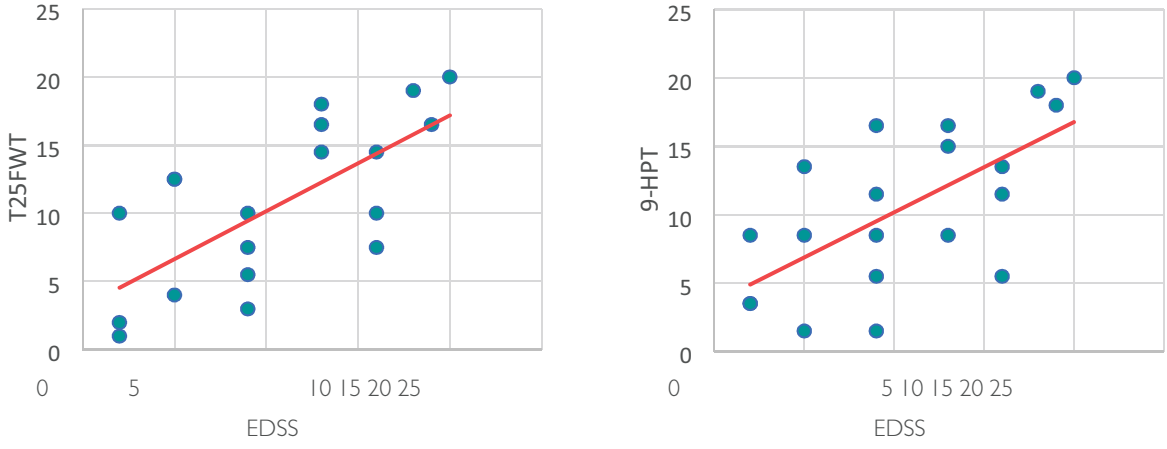

Figure 4 **Correlation of EDSS-T25FWT (left) and EDSS-9-HPT (right) one year later in patients on glatiramer-acetate therapy.**

There was a strong correlation between EDSS and T25FWT (rs=0.694) and EDSS and 9-HPT (rs=0.655), one year later in patients on glatiramer-acetate therapy.

DISCUSSION

Large studies have proven the effectiveness of immunomodulatory therapy in the treatment of multiple sclerosis primarily in reducing the number of relapses, reducing the progression of the disease, as well as slowing down the disability worsening (12). Therefore, the question arises as to which immunomodulatory therapy prescribe to the patient to stop the progression of the disease. An additional factor that is needed to take into account when choosing is the use of immunomodulatory therapy during pregnancy, pregnancy planning and during breastfeeding. Therefor we can see that 75 % of patients were female patients.

Statistical analysis proved that there was no statistically significant deviation from the expected distribution in the gender structure of the patients included in the study. In the total sample of patients, 70% (n=28) were female. According to the results of the Multiple Sclerosis Atlas, 69% of all patients diagnosed with multiple sclerosis were female, which was, 2 to 1 in favor of the female gender (11). Our results corespond with this data.

The mean age when multiple sclerosis was diagnosed for all 40 patients was 33.35±9.392 years. Patients treated with glatiramer-acetate, had mean age 36.35±7.686 years. According to the results of the Atlas of Multiple Sclerosis, the mean value of age at which multiple sclerosis is diagnosed is 32 (11).

The EDSS score used to describe the clinical disability of a patient with MS is a common parameter which is used for disease monitoring. In our sample, patients treated with glatirameracetate there is no statistically significant deviation from the expected distribution at the beginning of the observation period and after one year (p=0.749). In patients in the initial follow-up period, the mean arithmetic value of the EDSS score was 2.125±0.9442. After a year, the same value in patients on glatiramer-acetate therapy was 2.475±1.342, which is in favor of effectivnes of this treatment followed by EDS.

According to analysis that observed the effectiveness of GA, the EDSS score after 2 years of treatment of patients who were receiving GA, there was a statistically significant increase in the mean values of this scale (13). The results of this study should be considered with caution, due to the small number of patients included.

Brain magnetic resonance remains the basic imaging method for the diagnosis of multiple sclerosis. Brain MRI is a very sensitive method for determining disease activity, but in a large number of cases, patients may have brain MR activity without clinically clear symptoms (14). In our research, we followed 4 basic possibilities of lesions appearance on MRI: a) without activity and progression, b) with activity, without progression, c) without activity, with progression and d) with activity and progression. Most patients immunomodulators were without progression and activity on brain MRI (GA: 75%). 10% of patients treated with glatiramer-acetate had activity without progression. We have proven that there is no activity and progression of the disease on brain MRI (p=0.169) in patients aftter one year.

In a study comparing interferon-β 1b and glatiramer-acetate in both groups 23.2% of patients had a complete remission of the disease on magnetic resonance imaging of the brain (no activity I progression) after two years. In addition, 46.4% had incomplete remission (with/without progression with/without activity), while 30.4% never managed to reach remission (15). Cohan S, et al. in their study which also observed the effect of glatiramer acetate and interferon-β 1b and β 1a on activity and progression of the disease, stated that 16.7% of the 436 observed patients had some type of activity and/or progression on brain MRI (16).

In an important pilot trial of GA, 50 RRMS patients were divided into treatment and placebo groups, with patients individually matched for gender, relapse frequency and degree of disability before entering the study. The degree of disability was measured by EDSS. The treatment group received GA 20 mg daily for 2 years. The results showed clear benefit with GA. The proportions of relapse-free patients in the treatment and placebo groups were 56% and 26% (p = 0.045) respectively. The number of relapses in the treatment and placebo groups was 16 and 62. Interestingly, the less disabled patients had more benefit in the relapse rate than the more disabled patients, in the treatment group, suggesting a greater efficacy the earlier treatment is started (17).

Our research was conducted to evaluate the effectiveness of glatiramer-acetate through functional tests and activity on magnetic resonance imaging of the brain and it had several shortcomings that affected the statistical result itself. The EDSS scale, due to its predominantly bimodal results, has its limitations, so it is necessary to use other functional tests to assess the disability of patients. Also, some important functions such as the development of dementia, loss of vision or hand weakness may go unnoticed by the EDSS scale. For this reason, it is necessary to use other disease outcome measures in everyday clinical practice, for a better insight into the progression of the disease.

A small number of patients were included in the study, which consequently affected the results of the study. Also, a short time period of one year can have an impact on the research results. A longer period of time is needed to assess the reduction of disease progression with immunomodulatory therapy.

CONCLUSION

Results of this research clearly confirmed, by functional tests and MRI findings, previously proven good effectiveness of glatiramer acetate in the treatment of multiple sclerosis.

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Reprint requests and correspondence:
Admir Mehičević, MD
Clinic of Neurology
Clinical Centre University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina,
Phone: +387 33 298 094
Email: admirmehicevic@hotmail.com
ORCID ID: 0000-0001-6518-7441

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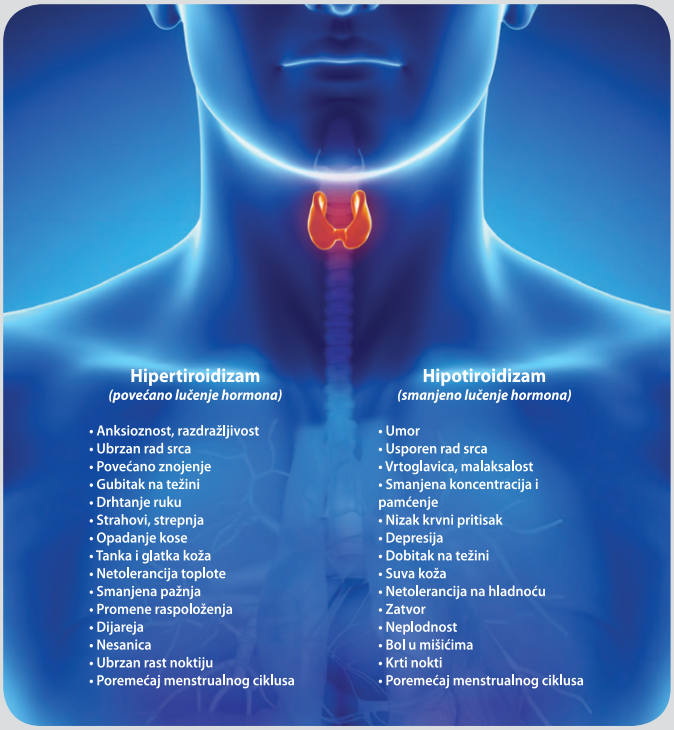

Correlation between forced expiratory volume in the first second and peak expiratory flow measured by peak flow meter in chronic obstructive pulmonary disease

Korelacija između forsiranog ekspiratornog volumena u prvoj sekundi i vršnog ekspiratornog protoka izmjerenog mjeračem vršnog protoka u hroničnoj opstruktivnoj plućnoj bolesti

Jasmina Mustafić-Pandžić [1*], Belma Paralija[1,2]

[1]Clinic of Lung Diseases and Tuberculosis, Clinical Centre University of Sarajevo, Bardakčije 90, 71000 Sarajevo, Bosnia and Herzegovina
[2]Faculty of Medicine, University of Sarajevo, Čekaluša 90, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: the basic characteristic of chronic obstructive pulmonary disease (COPD) is a persistent reduction of forced expiratory volume in the first second (FEV1) and the ratio of FEV1 to forced vital capacity (FVC). Exacerbation of COPD (ECOPD) is an important event during the course of the disease. There is a question of whether peak expiratory flow (PEF) is useful in a short-term evaluation of COPD, especially when spirometry is not available on a regular basis. Aim: to determine and compare the PEF values using a peak flow meter and the FEV1 measured with spirometry in a patient suffering from COPD. Materials and methods: the research is designed as a cross-sectional, clinical study. It included 120 patients suffering from COPD who gave informed consent for the participation in the study according to the Helsinki Declaration. The relationship between PEF measured by mini-Wright PEF meter and FEV1 measured by spirometry was tested. Results: PEF values measured by peak flow meter correlate with FEV1 values measured by spirometry in patients suffering from COPD ($r = 0.532$, $p < 0.001$). Conclusion: based on the research results, the measurement of PEF with a peak flow meter could be applicable even in primary health care, where spirometry is unavailable for monitoring COPD exacerbations.

Keywords: chronic obstructive lung disease, forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), peak flow meter, spirometry

SAŽETAK

Uvod: osnovno obilježje hronične opstruktivne plućne bolesti (hOPB) je trajno smanjenje forsiranog ekspiratornog volumena u prvoj sekundi (FEV1) i omjera FEV1 i forsiranog vitalnog kapaciteta (FVC). Egzacerbacija HOPB-a (ECOPD) važan je događaj tokom bolesti. Postavlja se pitanje je li vršni ekspiracijski protok (PEF) koristan u kratkoročnoj procjeni HOPB-a, osobito kada spirometrija nije dostupna redovito. Cilj: utvrditi i usporediti PEF vrijednosti pomoću peak flowmetra i FEV1 izmjeren spirometrijom u bolesnika s HOPB-om. Materijali i metode: istraživanje je zamišljeno kao presječna, klinička studija. Uključeno je 120 bolesnika s HOPB-om koji su dali informirani pristanak za sudjelovanje u studiji prema Helsinškoj deklaraciji. Testiran je odnos između PEF-a izmjerenog mini-Wright PEF-metrom i FEV1 izmjerenog spirometrijom. Rezultati: vrijednosti PEF-a izmjerene peakflowmetrom koreliraju s vrijednostima FEV1 izmjerenim spirometrijom u bolesnika s HOPB-om ($r = 0{,}532$, $p < 0{,}001$). Zaključak: na temelju rezultata istraživanja mjerenje PEF-a vršnim mjeračem protoka moglo bi biti primjenjivo čak I u primarnoj zdravstvenoj zaštiti, gdje spirometrija nije dostupna za praćenje egzacerbacija HOPB-a.

Ključne riječi: hronična opstruktivna bolest pluća, forsirani ekspiracijski volumen u 1 sekundi (FEV1), vršni ekspiracijski protok (PEF), vršni protok, spirometrija

INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) publishes an annual report that serves as a clinical guideline for the diagnosis and management of COPD worldwide and has very recently released the 2023 annual report. Chronic obstructive pulmonary disease (COPD) is defined as "a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure

to noxious particles or gases" (1,2). COPD is currently the third leading cause of death worldwide and has become an important public health problem (1).

COPD is complicated by frequent and recurrent acute exacerbations, which result in enormous healthcare expenditures and high morbidity. An exacerbation of COPD is defined as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum and beyond normal day-to-day variations, that is acute in onset and may warrant a change in regular medication in a patient with underlying COPD" (3,4,5).

Well-recognized and treated COPD might have clinical progression. Today's treatment includes treatment of symptoms, improving lung function, improving quality of life and reducing the frequency of disease exacerbations, as well as reducing the costs of the health system (6).

Monitoring of COPD is limited mainly to pulmonary function testing using office- or laboratory-based spirometry, without effective tools to objectively monitor disease activity at home on a day-to-day basis. In asthma patients, peak expiratory flow rate (PEF) measurement has been promoted as a useful tool for assessing airway obstruction and titrating therapy. It is not only cheap, but has high reproducibility and user compliance rates, making it a useful tool for ambulatory monitoring of asthma. In COPD, however, the utility of PEF monitoring remains unclear (7).

Spirometry is the cornerstone of COPD diagnosis. According to GOLD guidelines, persistent airflow limitation is defined as a post-bronchodilator ratio of FEV1 to Forced Vital Capacity (FEV1/FVC) of less than 0.7 (8).

PEF reflects the largest expiratory flow rate achieved with a maximally forced effort from a position of maximal inspiration that can be obtained during spirometric recordings (9).

A peak expiratory flow of < 80% predicted is the best cut-off to detect airflow limitation with 90% sensitivity, and 50% specificity, which further increase in symptomatic patients (10).

Current GOLD recommendations suggest that despite the good sensitivity, PEF measurements alone cannot reliably be used as the only diagnostic test for COPD due to the weak specificity. A positive association between exacerbation frequency and daily PEF variations has been reported, validating PEF measurements as a potential monitoring tool in COPD patients (9,11,12).

Our hypothesis was that PEF values reduction measured with a peak flow meter correlate with reduction of FEV1 values measured with spirometry in patients suffering from COPD. Values could be detected before ECOPD (An event characterized by dyspnea and/or cough and sputum that worsens over ≤14 days, which may be accompanied by tachypnea and/or tachycardia, and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways), and this may provide a predictive indicator for early detection and prevention before the onset ECOPD.

AIM

The aim of the study was to determine and compare the PEF values using a peak flow meter and the FEV1 measured with spirometry in a patient suffering from COPD

MATERIALS AND METHODS

The research was designed as a cross-sectional, clinical study and it was conducted over six months. The research included 120 patients suffering from COPD. Inclusion criteria were: 1 A clinical diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (1); 2 age > 50 years; 3 in a stable stage of the disease, with no history of exacerbations over the previous 8 weeks.

Patients with any other significant respiratory diseases (such as asthma, neuromuscular diseases, bronchiectasis, diseases of the diaphragm, cardiovascular diseases), and those unable to complete the study were excluded. All patients gave written informed consent according to the Helsinki Declaration to participate in the study after understanding the nature and purpose of the study.

Methods

PEF was calculated using a peak expiratory flow meter, which was given to patients who met study inclusion criteria. Clement Clarke peak flow meter made in England has a mouthpiece, an indicator, and numerical markings ranging from 60 to 800 L/min.

In accordance with the international guidelines the subjects performed at least three acceptable blows into the peak flow meter. An acceptable PEF value was defined as one that was produced with the hardest blow, after taking a maximum deep inhalation. The highest of the three acceptable readings was recorded as the PEF of the individual (13).

The PEF value was compared to the EU scale's reference values (15,16,17,18), which were developed and standardized based on the person's sex, height and age. A percentage of the patient's (best) predicted value, which is presented on the EU scale of reference values, is used to express the patient's current best value of PEF from three attempts.

PEF less than 80% of the predicted value for a certain person is considered an abnormal value, i.e., the presence of airway obstruction.

After 15 minutes, the subjects performed spirometry, which determines FEV1 in L/sec, but also expressed as a percentage in relation to the standardized predicted value of a certain individual according to gender, age and body weight.

The specified percentage values as well as the percentage ratio FEV1/FVC were automatically measured on the Jaeger device, Type flow screen 100-24=V,50/60Hz 60W.IP20 made in Germany.

The patient performed the test in a sitting, upright position with a clip on the nose and lips wrapped around the mouthpiece. After a deep inspiration, the patient exhaled as forcefully as possible into the mouthpiece of the spirometer (14). Based on the obtained values, the severity of COPD was determined according to the GOLD guidelines (1).

The percentage values of PEF measured by a peak flow meter were compared with the percentage values of FEV1 measured by spirometry using statistical methods.

Statistical analysis

Data were analysed using the SPSS Statistic v.21.0 for Windows. The data were presented in the form of tables and charts using classical methods of descriptive statistics and depending on the nature of the data and the measurement scale. Adequate methods

of classic descriptive statistics were used to describe the sample, depending on the nature of the data: Arithmetic mean (M), standard deviation (SD), median (Med), interquartile range (25th percentile and 75th percentile), absolute frequency (N) and relative frequency (%).

The examination of the continuous numerical variables distribution normality was carried out by inspection of histograms, quantile diagrams and formal testing using the Kolmogorov-Smirnov test. Analysis of categorical variables was performed using Pearson's x^2 test or Fischer's exact probability test. Analyses of normally distributed continuous ratio characteristics were performed using ONE-WAY ANOVA test and Independent simple T test for independent samples, while non-parametrically distributed numerical variables were analysed using Kruskal-Wallis H test and Mann-Whitney U test for independent samples. Pearson's and Spearman's rank correlation coefficient were used to test the linear relationship between proportional and ordinal characteristics. The threshold of statistical significance was set at the conventional level of $P \leq 0.05$ for omnibus tests, and for post hoc analyses, Bonferroni correction was performed to control the inflation of type I error due to multiple tests.

The measure of diagnostic accuracy (validity) is shown by the power of the analysis using the ROC curve analysis (*Receiver Operating Characteristic*), where spirometry (FEV1) is used as a reference method based on which we know for sure whether the disease is present or not.

RESULTS

Out of the total number of patients with COPD (*n*=120), 5 (4.2%) had mild COPD, 43 or 35.8% had moderate COPD, 51 or 42.5% had severe COPD, while 21 or 17.5% had very severe COPD (Table and Figure 1).

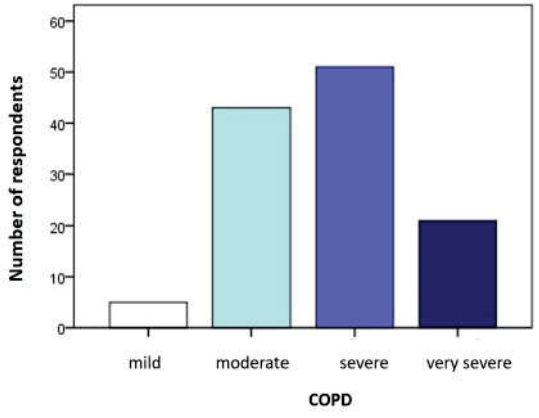

Figure 1 **Distribution of patients according to degree of COPD.**

Table 1 **Distribution of patients according to degree of COPD (n=120).**

COPD	Frequency	Percentage	Valid percentage	Cumulative percentage
MILD	5	4,2	4,2	4,2
MODERATE	43	35,8	35,8	40,0
SEVERE	51	42,5	42,5	82,5
VERY SEVERE	21	17,5	17,5	100,0
TOTAL	120	100,0	100,0	

Out of the total number of patients with mild or moderate COPD (n=48), 32 (66.7%) were female, and 16 (33.3%) were male. Out of the total number of patients with severe COPD (n=51), 21 (41.2%) were female and 30 (58.8%) were male, while out of a total of 21 patients with very severe COPD (n=5), 7 (33.3%) were female and 14 (66.7%) were male (Figure 2).

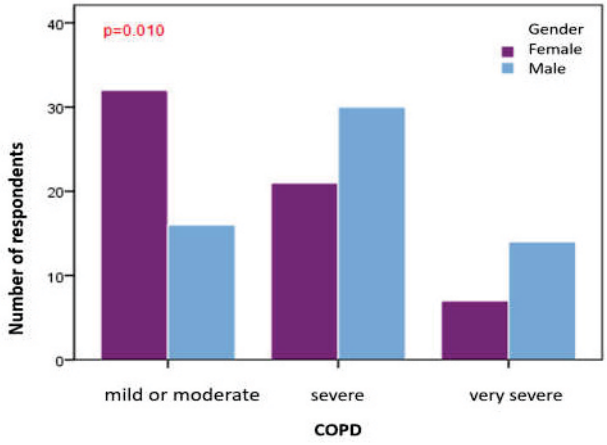

Figure 2 **Distribution of patients according to gender and degree of COPD.**

The value [$\chi 2(2) = 9.255$, $p=0.010$] is statistically significant, which indicates that the obtained differences between the observed groups of COPD according to gender were not obtained by chance. Analysis of the residuals indicates that patients with mild or moderate COPD had a high than expected representation of the female gender (3.0) and a lower representation of the male gender (-3.0) compared to severe and very severe COPD.

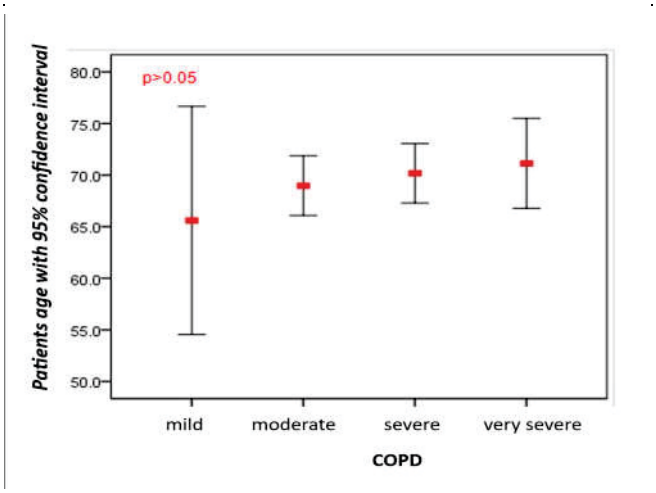

Figure 3 **Mean age of patients according to degree of COPD with 95% confidence interval.**

Patients with mild COPD had an average age of $\overline{U}$ = 65.6±8.9 years, while the average age of patients with moderate COPD was $\overline{U}$ = 69.0±9.4 years. Patients with severe COPD had an average age of $\overline{U}$ = 70.2± 10.2 years, while the average age of patients with very severe COPD was $\overline{U}$ = 71.1± 9.6 years. It is evident that patients with a more severe form of COPD are older, but the mentioned difference did not reach statistical significance [F (3) =0.562, p=0.640] (Figure 3).

In patients with mild COPD, the median was 64.9 (58.6-85.4) %, while in patients with moderate COPD, the median was 56.8 (41.8-72.9) %. Patients with severe COPD had a median of 38.8 (30.1-50.0) %, while patients with very severe COPD had a median of 32.7(23.6-42.1) % (Figure 4).

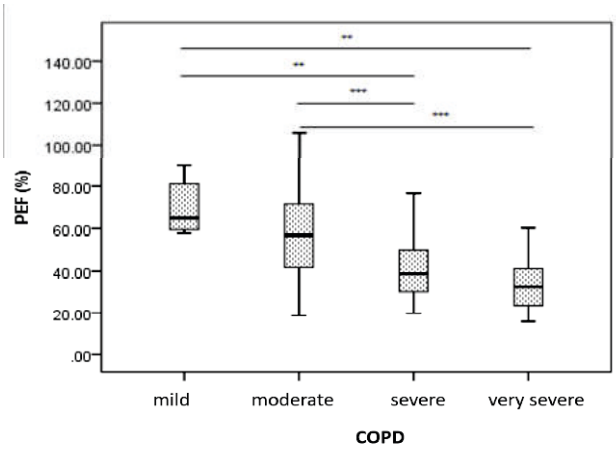

Figure 4 **The value of PEF according to the degree of COPD.**

Median PEF values decrease from mild COPD (64.9; 58.5-85.4) %, moderate COPD (56.8;41.8-72.9) %, severe COPD 38.8;30.1-50.0) % to very severe COPD (32.7;23.6-42.1) %. And the obtained difference is statistically significant, $\chi 2(3) = 31.255$, p< 0.001.

Statistical significance after adjustment was accepted at the level of p<0.008. Post hoc analysis established the existence of statistical significance between mild and severe (p=0.003), mild and very severe (p=0.001), moderate and severe (p<0.001), moderate and very severe (p<0.001), while no statistically significant difference was proven between the groups: mild and moderate (p=0.088), and severe and severe very severe (p=0.032) (Figure 4).

In patients with mild COPD, the median value of FEV1% was 88.8 (84.5-97.0) %, while in patients with moderate COPD the mean value of FEV1 was 62.0 (56.0-69.0) %. Patients with severe COPD had a median FEV1 value of 41.0 (37.0-45.0) %, while patients with very severe COPD had a median value of 25.0 (20.5-28.5) % (Figure 5, Figure 5.1).

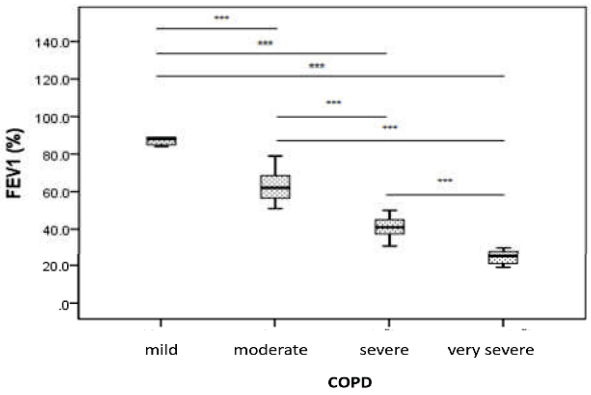

Figure 5 **Values of FEV1 according to the type of COPD.**

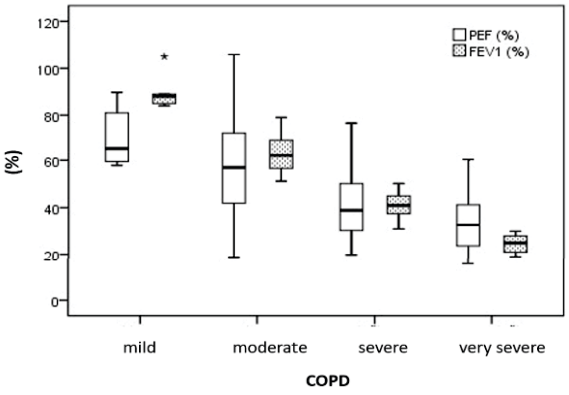

Figure 5.1 **PEF and FEV1 values according to degree of COPD.**

The median FEV1 (%) value decreases from mild COPD (88.8; 84.5-97.0) %, moderate COPD (62.0; 56.0-69.0) %, severe (41.0; 37.0-45.0) %, to very severe (25.0; 20.5-28.5) %, and the obtained difference is statistically significant, $\chi 2(3) = 103.814$, p< 0.001.

Post hoc analysis determined the existence of statistical significance between mild and moderate (p<0.001), mild and severe (p<0.001), mild and very severe (p<0.001), moderate and severe (p<0.001), moderate and very severe (p<0.001), and severe and very severe COPD (p<0.001).

There is a statistically significant positive correlation between the value of PEF (%) and FEV1 (%), *Rho*=0.532, *p*<0.001 (Figure 6).

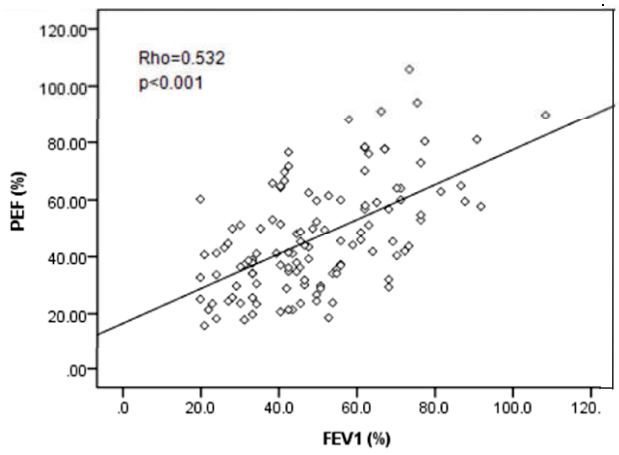

Figure 6 **Relationship between PEF and FEV1.**

DISCUSSION

Out of the total number of participants in our study with COPD, 54 were women and 62 were men. Women are more prevalent in the mild and moderate COPD groups than in the severe and very severe COPD groups. Men are presented more frequently.

Between the studied groups, there is a statistically significant variation in the proportion of male and female patients [$\chi^{2(3)}$=9.623, P=0.018] (Table 1).

Smoking has been a major factor in the onset and progression of COPD since the 1940s, particularly in women (18).

Pre-existing asthma (19), polluted air at home or at work, and respiratory infections (20) are further risk factors.

In contrast to men, women with COPD in the US experienced an increase in hospitalizations and mortality.

Dyspnea and physical restrictions are more prevalent in women with COPD than in men with COPD, according to Lopez Varela MV, et al. (21) in the PLATINO study, which they conducted after observing a healthy population and people with COPD.

Menses AM, et al (22) in a Platino study examined the prevalence of COPD in the five largest Latin American countries. They found data that the prevalence of COPD increases with age and that it is highest in people over 60 years old. In this study, patients with mild COPD had an average age of $\overline{\mu}$ =65.6±8.9 years, while the average age of patients with moderately severe COPD was $\overline{\mu}$ =69.0 ± 9.4 years.

Patients with severe COPD had an average age of $\overline{\mu}$ =70.2 ± 10.2 years, while the average age of patients with very severe COPD was $\overline{\mu}$ =71.1 ± 9.6 years. It is evident that patients with a more severe form of COPD are older, but the mentioned difference did not reach statistical significance [F (3) = 0.562, P=0.640].

The British Thoracic Society and later the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) based their negative views on PEF as a clinical test in COPD on research that speaks of the unreliability of PEF to adequately assess lung function in COPD (23). In patients with obstructive lung diseases, the PEF and FEV1 parameters have long been used to assess lung damage. With COPD, FEV1 is preferred because it represents the gold standard in the diagnosis of COPD according to GOLD. However, spirometry is not always available in developing countries, and there is a need to evaluate the information that can be obtained through PEF measured with a peak flow meter. In this research, the usability of the PEF is compared to that of the measuring peak flow meter in defining the severity of the air flow obstruction.

Rauf-ul-Hassan M, et al. (24) investigated the relationship between FEV1 and PEF in patients with obstructive lung disease. The research included 120 subjects who were diagnosed with asthma and COPD, and FEV1 and PEF were measured with an electronic spirometer. Pearson's correlation coefficient was 0.798 (p <0.05). They believe that PEF is not useful in the diagnosis of COPD and explain their results by the pathophysiological changes that occur in COPD, but they did not clearly specify which patients had asthma and which patients suffered from COPD (24). Namely, PEF is recorded in the first tenth of a second of forced exhalation, while FEV1 continues to record forced exhalation for another 0.9 seconds. During exhalation, the volume of exhaled air decreases, and at the same time, the air flow decreases. FEV1 records what happens to the exhaled air after the exhalation speed is reached.

A sudden drop in exhalation occurs due to structural damage caused by COPD. The loss of the parenchymal structure of the lungs due to chronic inflammatory processes in COPD destabilizes the elastic support of the small airways. An increase in intrathoracic pressure at the time of exhalation causes the collapse of the small airways; air is trapped in the alveoli and exhalation is prevented, which leads to a sudden drop in the air flow rate. This damage is irreversible and progressive. However, this is a pathological process that is measured by spirometry, not PEF.

For this reason, FEV1/FVC is the diagnostic test of choice in COPD. However, our study raises the question of whether PEF can be used as a parameter for monitoring COPD rather than as a parameter for diagnosing COPD.

In our study, the Scatter plot of the relationship is between the values of PEF (%) and FEV1 (%), r(118) = 0.532, P<0.001 (Figure 6.).

Our results are supported by the reports of White P, (23), who states that acute exacerbations lead to an increase in mucus inflammation and muscle spasm and that there are other factors in COPD that are considered important, such as inspiratory reserve volume, vital capacity, acute changes as a result of infection, and deterioration in relation to the diameter of the airways. Although the partial irreversibility of symptoms is the pathological basis of COPD and is different from the reversibility of asthma, it is nevertheless a key dynamic factor in the diameter of the airways. According to White, PEF should not be less useful in measuring airway caliber in COPD as opposed to asthma (23).

Aggarwal AN, et al. (12) investigated the relationship between FEV1 and PEF in patients with air obstruction. In the research, out of the 25,914 spirometry findings reviewed, 6,167 findings were included, which represented the database for further analysis. After data processing, there was a moderate correlation between FEV1 and PEF (%), with a Pearson correlation coefficient of 0.768 (p 0.001) between men and women alike. They state that the numerical summarization of information does not imply that PEF can be used as a substitute for FEV1 and that scatter plots from different reports show a significant difference in the values of FEV1 (%) and PEF (%) in individual patients, although many coordinates lie close to the line of identity.

In our research, it was shown that the connection is linear, which was determined by visual analysis of scatter plots, and that there is a highly statistically significant moderate to relatively strong positive correlation between PEF (%) and FEV1 (%). In our study, the median value of PEF compared to the median FEV1 had a lower value in patients with mild COPD (64.9 vs. 88), moderate COPD (56.8 vs. 62.0), and severe COPD (38.8 vs. 41, 0), whereas in patients with very severe COPD, the median PEF would be higher compared to the median FEV1 (32.7 vs. 25.0). Aggarwal AN, et al. (12) also found results that showed that in patients with FEV1 >40%, PEF tended to exceed FEV1. And in patients with severe obstruction, PEF tended to underestimate FEV1. Other researchers have reached similar results.

In his reports, Whites P, (24) explains why PEF can occur as equal to or greater than the predicted values for age, sex, and height in a patient whose FEV1 is greater than predicted. Namely, in Great Britain, the Association for Respiratory Technology and Physiology collects and approves the predicted PEF values, which are taken from the research of the European Community for coal and steel. The equations from which their values derive significantly reduce the predicted values in adults compared to the Nunn and Greg equations, i.e., the equations that were used in our research and which the ERS (European Respiratory Society); now prefers. They caused PEF to be presented in the final reports from the pulmonary laboratory as equal to or greater than predicted values for age, gender, and height in patients with FEV1 lower than predicted. In this way, they reduced physicians' belief in PEF as a test. Another problem is the inaccuracy of the measuring scale used on European devices for measuring peak air flow.

Miller MR, et al. (25) pointed out that the measuring devices have characteristic profile errors. Devices read the air flow rate less at low and high flow frequencies and read the flow rate higher in the middle range.

These errors, as White P, (23) states, can be easily corrected mathematically, and the American Thoracic Society, which approved the refinement of the scale for measuring peak air flow, made it possible to obtain them in North America. The failure to correct the scale for peak flow meters in Europe is a result of difficulties in harmonizing policies regarding peak flow meter standards in the European Union. In our research, it was proven that there is a highly statistically significant moderate to relatively strong positive correlation between the values of PEF and FEV1 (%), r (118 = 0.532, P<0.001) (Figure 6.)

Similar results were obtained by many other researchers. Thiadens HA, et al. (26) also investigated the utility of PEF measurement in the verification of airway obstruction and bronchodilator response compared to FEV1 in primary practice. Their research included 240 respondents, aged between 18-75 years, who had had a cough for the past two weeks. They used questionnaires, physical examinations, and spirometry. In their results, the correlation between the absolute values of PEF and FEV1 was shown to be very high (r=0.82, p<0.001). They came to the conclusion that by measuring PEF, broncho-obstruction can be ruled out, but it cannot be used to diagnose obstructive diseases in primary care. However, in their research, they did not measure PEF with a peak air flow meter but with an electronic spirometer, which did not clearly prove the absence of COPD.

In their research, Emerman CL, et al. (27) investigated the use of PEF in ECOPD in emergency centers. They compared PEF with FEV1 as a parameter of airway obstruction in acute ECOPD. The study included 199 subjects over 50 years of age with verified ECOPD. The values of PEF and FEV1, which were measured by an electronic spirometer, were compared as absolute values and converted into percentages of predicted values. Through research, they obtained a strong correlation between PEF and FEV1 in absolute values (r = 81; p<0.0001) and in percentages of pre-values (r= 81; p<0.0001). They came to the conclusion that PEF can be used as an alternative measurement of airway obstruction in acute asthma in conditions when FEV1 is not available.

Dekker FW, et al. (28) examined the validity of PEF in measuring the reversibility of airway obstruction in people with a positive history of asthma and COPD. 123 subjects between the ages of 40-84 were included in the research. PEF was measured with a mini Wright peak flow meter before and after the application of 400 ug of inhaled Salbutamol. Changes in PEF were compared with changes in FEV1 measured by spirometry. The results stated that there was a moderate correlation between PEF and FEV1, and based on this, they concluded that the peak flow meter was useful in diagnosing the reversibility of airway obstruction in people with asthma and COPD.

Vaughan MTR, et al. (29) examined the relationship between PEF and FEV1 in patients with verified asthma as well as other obstructive diseases with varying degrees of air obstruction. The study included 102 subjects. PEF was measured with a peak flow meter and FEV1 was measured with an electronic spirometer.

After PEF and FEV1 values were converted into percentage predictive values after data processing, a strong correlation was obtained between FEV1 and PEF, r = 0.846 (P<0.001). These researchers came to the conclusion that PEF values are higher than FEV1 values by 16%; that is, there is a correlation, but it is not usable in clinical practice. In this research, it is not clearly specified which patients had COPD. Kelly CA, et al (30) investigated the therapy, and PEF was measured 2-4 times a day, while FEV1 was measured once daily. The comparison is between absolute values that were later converted into percentage predictive values.

The results showed a strong correlation between the absolute values of PEF and FEV1, r=0.95 (P<0.001), while the percentage predictive values between PEF and FEV1 were r=0.91 (P<0.001). Jackson H, et al. (31), in their study, stated that general practitioners were more familiar with the possibilities of PEF measured with a peak flow meter and questioned the use of complex spirometric tests in identifying chronic obstructive pulmonary disease. In their study, they measured FEV1 by spirometry using a PEF peak flow meter and used anamnestic data on smoking and respiratory symptoms. They came to the conclusion that measuring PEF is a very sensitive method and an accurate index of airway obstruction, as well as a sensitive indicator of measuring the strength of the respiratory muscles. They proved that a PEF of less than 80% can detect 91% of all people with COPD, and the sensitivity of this method for moderate and severe COPD is 100%. However, the specificity of this test is limited and amounts to 82%.

The higher prevalence of smokers and those with airway obstruction in the false-positive group suggests that it is possible that a PEF of less than 80% refers to milder forms of COPD (31). In our research, the sensitivity of the test in detecting mild or moderate COPD is 60.4%; that is, the PEF finding is capable of identifying in 60.4% of patients with COPD people who really have mild or moderate COPD and recognizing people who really do not have mild or moderate COPD. The sensitivity of the test in the detection of really severe COPD is 82.4%; that is, the PEF finding is capable of identifying people who really have very severe COPD in 82.4% of patients with COPD. The specificity of the test is 85.7%,

i.e. the finding is capable of recognizing people who really do not have COPD in 85.7% of patients with COPD.

The fact is that there is no clearly defined objective strategy for classifying the severity of airflow obstruction based on FEV1 (%) values in COPD; namely the GOLD guidelines divide COPD into mild, moderately severe and very severe according to the British Thoracic Society (60 %-40%), American Thoracic Society (50%-35%), European Thoracic Society (70%-50%) and the new American Thoracic Society/European Thoracic Society (80%-50%) (12).

CONCLUSION

Based on our results, comparing PEF with FEV, we classified COPD based on the PEF value into the following categories: Mild or moderate COPD: PEF>52.39% (Sn= 60.4%; Sp = 84.71%); Severe COPD: PEF< =53.16 (Sn=82.4%; Sp=42.0%); Very severe COPD: PEF <= 44.64% (Sn=85.7%; Sp=52.5%). Based on this classification, we proved that the condition of COPD can be monitored using a peak flow meter but not used in the diagnosis of COPD, as already stated in the GOLD guidelines 2023. PEF values measured by peak flow meter correlate with FEV1 values measured by spirometry in patients suffering from COPD. Based on the research results, the measurement of PEF with a peak flow meter could be applicable even in primary health care, where spirometry is unavailable for monitoring COPD exacerbations.

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Reprint requests and correspondence:
Jasmina Mustafić-Pandžić, MD
Clinic of Lung Diseases and Tuberculosis
Clinical Center University of Sarajevo
Bardakčije 90, 71000 Sarajevo
Bosnia and Herzegovina
Email:jasminamustafic@hotmail.com
ORCID ID: 0009-0009-4074-151X

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Is there a difference in lifestyle and cardiovascular risk factors among medical staff and general population?

Postoji li razlika u životnom stilu kardiovaskularnih rizika između medicinskih radnika i opće populacije?

Slavenka Štraus*, Muhamed Djedović, Ilirijana Haxhibeqiri-Karabdić, Sanja Granov, Amel Hadžimehmedagić

Clinic of Cardiovascular Surgery, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: cardiovascular diseases (CVDs) remain the leading cause of worldwide mortality, leading cause of death and disability globally with over 17.9 million deaths in 2019, representing 32% of all deaths, and 38% of premature deaths from non-communicable diseases. Thousands of studies support the concept that controlling lifestyle risk factors for CVDs such as regular physical activity, maintenance of a proper weight, sound nutritional practices, avoiding tobacco and alcohol abuse, all significantly reduce the risk of CVD. Aim: to compare the prevalence of lifestyle risk factors for CVDs in healthcare and non-healthcare workers. Materials and methods: the study included one hundred and twenty participants, divided into two groups, medical staff group (doctors and nurses) with 60 participants and non-medical group (teachers and professors) with 60 participants as well. Based on the collected data from the questionnaire created for this purpose, the following results were obtained. Results: both observed groups were similar in sociodemographic data as well as in the presence of comorbidities. Our study confirmed that medical staff as well as non-medical, had BMI in normal range, though the value varied in medical staff group from 20.5 to 34.0 kg/m^2 and in non-medical group from 18.5 to 34.9 kg/m^2, with a mean value of 24.82 kg/m^2. There was a difference in heredity, in medical staff group it was presented in 48.3% compared with non-medical group with 35%, but there was no statistically significant difference. Statistical difference between groups was observed in tobacco use, there were more smokers in the medical staff group 46.7%, compared to non-medical group, where the percentage of smokers was 26.7% which gives a statistically significant difference (P = 0.037). Also, In the medical staff group only 15% of participants were physically active, while that percentage in non-medical group was 35% (P=0.020). Conclusion: in order to obtain a better and more comprehensive profile of the presence of lifestyle risk factors for CVD in the population of medical workers, it would be necessary to conduct a study with a larger number of participants and add the way of nutrition and the existence of stress, which would process the risk factors more comprehensively.

Keywords: cardiovascular diseases, medical staff, lifestyle-associated risk, prevalence

SAŽETAK

Uvod: kardiovaskularne bolesti (KVB) ostaju vodeći uzrok smrtnosti širom svijeta, vodeći uzrok smrti i invaliditeta na globalnom nivou sa preko 17,9 miliona smrtnih slučajeva u 2019. godini, što predstavlja 32% svih smrtnih slučajeva i 38% prijevremenih smrti od nezaraznih bolesti. Hiljade studija podržavaju koncept da kontrolisanje faktora rizika za KVB u načinu života, kao što su redovna fizička aktivnost, održavanje odgovarajuće težine, zdrava ishrana, izbegavanje zloupotrebe duvana i alkohola, značajno smanjuju rizik od KVB. Cilj: da se uporedi prevalenca životnih faktora rizika za KVB kod zdravstvenih radnika i opće populacije. Materijali i metode: studiji je pristupilo 120 osoba, podeljenih u dve grupe, grupu medicinskog osoblja (doktori i medicinske sestre) sa 60 učesnika i nemedicinsku grupu (nastavnici i profesori) takođe 60 učesnika. Na osnovu prikupljenih podataka iz upitnika kreiranog za ovu svrhu, dobijeni su sljedeći rezultati. Rezultati: obje posmatrane grupe bile su slične po sociodemografskim podacima kao i u prisustvu komorbiditeta. Naša studija je potvrdila da medicinsko osoblje, kao i nemedicinsko, ima BMI u normalnom rasponu, iako je vrijednost varirala u grupi medicinskog osoblja od 20,5 do 34,0 kg/m^2 i u nemedicinskoj grupi od 18,5 do 34,9 kg/m^2, sa srednja vrijednost 24,82 kg/m^2. Postojala je razlika u nasljeđu, u grupi medicinskog osoblja je predstavljena sa 48,3% u odnosu na nemedicinsku grupu sa 35%, ali nije bilo statistički značajne razlike. Statistička razlika između grupa uočena je u upotrebi duvana, više pušača je bilo u grupi medicinskog osoblja 46,7%, u odnosu na nemedicinsku grupu, gde je procenat pušača bio 26,7%, što daje statistički značajnu razliku (P=0,037). Takođe, u grupi medicinskog osoblja samo 15% učesnika je bilo fizički aktivno, dok je taj procenat u grupi nemedicinskog osoblja 35% (P = 0,020). Zaključak: kako bi se dobio bolji i sveobuhvatniji profil prisustva faktora rizika za KVB u populaciji medicinskih radnika, bilo bi potrebno provesti istraživanje sa većim brojem učesnika i dodati način ishrane i postojanje stresa, koji bi sveobuhvatnije obradio faktore rizika.

Ključne riječi: kardiovaskularne bolesti, medicinsko osoblje, riziko faktori i stil života, prevalenca

INTRODUCTION

Lifestyle diseases characterize those diseases whose occurrence is primarily based on the daily habits of people and are the result of an inappropriate relationship of people with their environment. Lifestyles are born of a multitude of causes, from childhood determinants to personality makeup to influences in the cultural, physical, economic, and political environments. In recent times, these lifestyle patterns have modified significantly which has led to increasing both physical and mental diseases in the world population.

Lifestyle diseases such as stroke, cancer, heart disease are by far the leading causes of mortality in the world, causing an estimated 35 million deaths, representing 60% of all deaths. About a quarter of these deaths were in low and middle-income countries (1). Also, cardiovascular disease (CVD) is the leading cause of death in most developed countries. Moreover, cardiovascular death has been shown to be the leading cause of death among physicians in the United Kingdom and United States. Although physicians' personal health practices are generally good, they often favor their professional obligations over their own health (2). As developing countries experience rapid urbanization, citizens are failing to maintain healthy diets or adequate levels of physical activity. The chronic diseases are mainly being caused by a small number of shared risk factors: improper diet, inadequate physical activity, tobacco use and excessive alcohol consumption. Medical staff should be mentors to general populations for a healthy life. Life style disorders are not just limited to the general population but even the doctors and nurses who guide them on their prevention are also getting victimized (1).

Lifestyle risk factors for CVD can be modifiable or non-modifiable. In the unmodified group there is gender, race, familiar hereditary predisposition and older age. The modifiable lifestyle risk factors include overweight, stress, lack of physical activity, unhealthy diet, alcohol abuse, smoking, high blood pressure, high cholesterol and diabetes.

All the previously mentioned variable lifestyle risk factors will lead to the occurrence of increased insulin resistance, increased sympathetic activation, endothelial dysfunction, increased inflammation, increased atherosclerosis, higher oxidative stress, everything that will lead to the onset of CVD (3).

The strength of the scientific literature supporting the health promoting impact of positive daily habits and actions avoiding lifestyle risk factors for CVD has been underscored by their inclusion in virtually every evidence based clinical guideline addressing the prevention and treatment of metabolically related diseases. These principles are also incorporated in numerous documents and guidelines from many heart and cardiology associations. Despite overwhelming evidence that lifestyle factors significantly affect short- and long-term health and quality of life, it has been frustratingly difficult to help people adopt these habits and practices (4).

For example, both overweight and obesity represent significant risk factors for CVD. The AHA lists obesity as a major risk factor for CVD not only because of its association with other risk factors (e.g. diabetes, dyslipidemias, elevated blood pressure, metabolic syndrome) but also because it serves as an independent risk factor. Distribution of body fat also carries an additional risk since abdominal obesity is an independent risk factor for cardiac disease. The accumulation of intra-abdominal fat promotes insulin resistance, which can lead to glucose intolerance, elevated triglycerides, and low HDL as well as hypertension (5).

Overwhelming evidence exists from multiple sources that cigarette smoking significantly increases the risk of both heart disease and stroke. This evidence has been extensively summarized elsewhere and is incorporated as a recommendation in the AHA 2020 Strategic Plan.

Elevated blood pressure represents a significant risk factor for both CVD and stroke. Issues related to the optimum levels of blood pressure control have been somewhat controversial. The Joint National Commission VII (JNC VII) defined a normal blood pressure as <120/<80 mm Hg and defined 80 to 89 mm Hg diastolic and 120 to 139 mm Hg systolic as prehypertension. Levels >140 mm Hg systolic and >90 mm Hg diastolic were classified as "hypertension." These recommendations were also incorporated into the AHA 2020 Strategic Plan (6).

Dietary management of blood lipids has been a mainstay, along with pharmaceutical therapy, for many years. The 2013 AHA/ACC Lifestyle Medicine Guidelines for Nutrition, as a component of managing blood lipids, advocates a diet consisting of vegetables, fruits, and whole grains, including low fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts, while limiting sweets, sugar-sweetened beverages, and red meat. This is the same dietary pattern that is recommended to lower blood pressure. These guidelines also emphasize adapting this dietary pattern to the appropriate caloric requirements as well as personal and cultural food preferences while also advocating medical nutritional therapy (MNT) for other medical conditions (including diabetes mellitus).

Diabetes is a recognized and significant risk factor for CVD, and it is the leading cause of morbidity and mortality among individuals with diabetes. Lifestyle therapies, including proper nutrition and regular physical activity, are key therapeutic modalities to reduce the risk of CVD in individuals with diabetes. Genetic factors likely play some role in high blood pressure, heart disease, and other related conditions. However, it is also likely that people with a family history of heart disease share common environments and other factors that may increase their risk. The risk for heart disease can increase even more when heredity combines with unhealthy lifestyle choices, such as smoking cigarettes and eating an unhealthy diet (7).

Finding Galen's statement, as early as in the 2nd century A.D., where Galen claimed that "the physician will hardly be thought very careful of the health of his patient if he neglects his own", prompted us to examine how much medical staff is exposed to lifestyle risk factors for CVD compared to the general population.

AIM

The aim of our research was to analyze risk factors for cardiovascular diseases related to lifestyle in the group of health care workers, doctors and nurses, compared to the general population, which in this study was represented with teaching staff.

MATERIALS AND METHODS

The study was conducted in the period between October 2022 and March 2023. The medical staff was employees of two Clinics of the Clinical Center University of Sarajevo, and the teaching staff was from three elementary schools in the Canton of Sarajevo. After a conversation with the participants of our study, in which the goal of the study was explained and how to fill out the

form, each of the participants, who agreed to participate in the study, filled out questionnaire and handed the form to the examiner.

We observed 120 participants divided into two groups. One group was medical staff with 60 participants, doctors and nurses, and the other 60 participants were teaching staff from primary schools, representing the group of non-medical workers, i.e. the general population.

For our research, a special questionnaire was created that contained numerous questions. The first part of the questionnaire was related to sociodemographic data such as age (in years), gender, academic degree, civil status, last measurement of weight in kilograms and height in centimeters in order to calculate body mass index (BMI). Obesity was defined as a BMI of at least 30 kg/m^2 whereas BMI values ranging from 25.0 to 29,9 kg/m^2 were indicative of overweight. In the second part of the questionnaire information regarding established cardiovascular risk factors was obtained, which included hypertension (currently on antihypertensive medication were considered hypertension), diabetes mellitus (verified on antihyperglycemic therapy, oral or otherwise), smoking habits (currently smoking at least 10 cigarettes per day), physical activity habits (aerobic exercises up to 60 minutes twice a week, walk every day for an hour were considered as regular exercise), alcohol consumption (more than two drinks per day for men and one drink per day for women) and presence of elevated cholesterol (all cholesterol levels above 5.0 mmol/l were considered increased). The third part of the questionnaire contained questions related to existing comorbidities (previous myocardial infarction, angina pectoris, stroke, peripheral vascular diseases, thyroid gland, lumbago, arthritis, gastrointestinal diseases, allergy) and a question about the presence of heredity for cardiovascular disease.

Statistical analysis

Baseline characteristics were collected and presented as a number of cases and percentage representation. Categorical values were analyzed with the $\chi 2$ test and Fisher's test. Student's T-test and Mann-Whitney U test were used to analyze quantitative values. Statistical hypotheses were tested at the level of α=0.05, i.e. the difference between samples was considered significant if P 0.05. Statistical analyzes were performed using IBM SPSS Statistics ver. 21.0.

RESULTS

The total number of the study participants was 120. They were divided into two groups; medical staff and a non-medical staff group. Both groups had the same number of participants, 60 each.

Table 1 represents the sociodemographic data. An average age of medical staff was 37.7±9.35 years, while in non-medical staff group was higher, 41.18 ±8.94 years. The ratio of men and women was equal in both observed groups, 75% female and 25% males. There was a statistic difference in marital status, more married participants in non-medical staff group 36.7%, compared with medical staffgroup 25% (P = 0.026).

Also, in terms of education, there was a significant difference. In the group of medical staff there were 44.7% with University education, while in the non-medical group, 65% were with University education (P=0.017). With High school education there was 58.3% in the medical staffgroup and 35% in the non-medical group.

Body Mass Index values in both observed groups were almost equal. Values of BMI ranged from 18.5 kg/m^2 to 34.9 kg/m^2, with a mean value of 24.82 kg/m^2.

Table 1 **Socio – demographic data and body mass index.**

Variable	Total (120)	Group 1 Medical staff (60)	Group 2 Non-medical staff (60)	P
Age (years)	22-66 39.44±9.27	22-62 37.7±9.35	26-64 41.18 ±8.94	**0.039***
Gender Female Male	 90 (75%) 30 (25%)	 45 (75%) 15 (25%)	 45 (75%) 15 (25%)	 1
Marrital status	37 (30.8%)	15 (25%)	22 (36.7%)	**0.026***
Education HSG UG	 64 (53.3%) 56 (46.7%)	 25 (44.7%) 35 (58.3%)	 39 (65%) 21 (35%)	 **0.017***
Children	77 (64.2%)	37 (61.7%)	40 (66.7%)	0.073
BMI (kg/m^2)	18.5-34.9 22.56±3.28	20.5-34.0 24.82±3.06	18.5-34.9 24.3±3.48	0.220

HSG – High school graduate, UG – University graduate, BMI – Body mass index
**P value < 0.05 is considered significant*

Table 2 provides data on the comorbidities of our observed study participants. In both observed groups, no previous heart attacks or strokes were diagnosed. Angina pectoris was verified in the 3 participants in the medical staffgroup.

Other observed comorbidities such as peripheral vascular diseases, arthritis, lumbago, gastrointestinal disorders and allergies were noticed in both groups with quite similar number of participants.

In the medical staffgroup there were 48.3% of positive heredity for cardiovascular diseases, in comparison with 35% in the non-medical group, which gives us a certain difference, but not statistically significant (P = 0.195).

Table 2 **Comorbidities.**

Variable	Total (120)	Group 1 Medical staff (60)	Group 2 Non-medical staff (60)	P
Myocardial infarction	0 (0%)	0 (0%)	0 (0%)	NS
Stroke	0 (0%)	0 (0%)	0 (0%)	NS
PVD	15 (12.5%)	9 (15%)	6 (10%)	0.582
HCVD	50 (41.7%)	29 (48.3%)	21 (35%)	0.195
Angina pectoris	3 (2.5%)	3 (5%)	0 (0%)	0.244
Arthritis	16 (13.3%)	8 (13.3%)	8 (13.3%)	1
Lumbago	47 (39.2%)	29 (48.3%)	18 (30%)	0.061
GID	30 (25%)	12 (20%)	18 (30%)	0.292
Allergies	39 (32.5%)	21 (35%)	18 (30%)	0.697

PVD - Peripheral vascular diseases, HCVD - Heredity for cardiovascular disease, GID – gastrointestinal disease
NS- non significant

The lifestyle risk factors for cardiovascular diseases of our participants are shown in Table 3. In terms of the observed risk factors, there was no significant statistical difference except in smoking and physical activity. Unfortunately, there were more smokers in the medical staff group 46.7%, compared to the non-medical group, where the percentage of smokers was 26.7% which gives a statistically significant difference (P = 0.037).

In the medical staff group only 15% of participants were physically active, while that percentage in the non-medical group was 35% (P = 0.020).

Self-reported hypertension, diabetes mellitus, hyperlipidemia and alcohol consumption did not show a significant difference between the observed groups.

Table 3 **Risk factors.**

Variable	Total (120)	Group 1 Medical staff (60)	Groupa 2 Non-medical staff (60)	P
HTA	18 (15%)	8 (13.3%)	10 (16.7%)	0.779
DM	8 (6.7%)	7 (11.7%)	1 (1.7%)	0.06
HLP	39 (32.5%)	24 (40%)	15 (25%)	0.119
Smoking	44 (36.7)	28 (46.7%)	16 (26.7%)	**0.037***
Alcohol	13 (10.8%)	8 (13.3%)	5 (8.3%)	0.557
Physical activity	30 (25%)	9 (15%)	21 (35%)	**0.020***

HTA – Hypertension, DM – Diabetes mellitus, HLP – Hyperlipidemia
**P<0.05 is considered statistically significant*

DISCUSSION

Cardiovascular disease (CVD), the most important chronic disease and the most common health problem around the globe, constitutes the most common cause of premature death and disability and is responsible for 35% of the death rate in developed countries and 30% of all deaths in the world. Projections show that an estimated 23.3 million people will die of CVD in 2030. However, research indicates that 75% of CVD mortality could be decreased with appropriate lifestyle changes. The most important risk factors proven to play a role in CVD include smoking, high levels of blood lipids, hypertension, stress, diabetes mellitus, malnutrition, and obesity. These risk factors account for approximately 80% of cases of CVD (8).

Several researchers have investigated the relationship between sedentary behavior and CVD. Young et al. conducted a study on 82,695 men aged ≥ 45 years and found that the hazard ratio of heart failure increased as the physical activity decreased, while Gobbo et al. concluded that the adherence to a few modifiable risk factors, such as physical activity, moderate alcohol consumption, not smoking, and avoiding obesity, reduced the risk of incident heart failure in 50% of cases (9).

Arterial hypertension and endothelial growth factor-linked polymorphisms are reported to contribute to vascular damage. Nicoll et al. studied 15,769 patients on the relationships between conventional CVD risk factors (age, gender, ethnicity, DM, dyslipidemia, hypertension, obesity, exercise) and coronary artery calcification, and found that hypertension and diabetes have the strongest association with coronary artery calcification. In addition to hypertension, smoking was considered as one of the key factors increasing the risk of vascular diseases but smoking also can produce DNA mutations in lung cells that increase the risk of lung cancer (10).

Obesity has become a global concern known as "globesity". According to WHO, about 13% of the world's adult population was obese in 2016. Besides CVD, several chronic diseases linked to obesity such as type II diabetes, hypertension, musculoskeletal disorders, and certain types of cancer (11).

Together with the obesity epidemic, type II diabetes has become a public health challenge in many countries. The combination of a sedentary lifestyle, unhealthy diets, overweight/obesity, smoking, and excessive alcohol intake are presumed responsible for 90% of type II diabetes. Furthermore, type II diabetes reported being among the leading causes of

blindness and lower limb amputation, in addition to being a significant risk factor for CVD.

Atherosclerosis is the leading cause of mortality globally, as it is the leading cause of fatal cardiovascular events, connected with existing dyslipidemia. WHO reported that 1/3 of ischemic heart disease is due to high lipids. Since lifestyle modifications do not cause a significant improvement in lipid profile, and the use of drugs can have adverse side effects (especially for low-risk patients), non-pharmacological alternatives for dyslipidemia control is gaining attention (12).

There was a difference in heredity, in the medical staffgroup it was presented in 48.3% compared with the non-medical group with 35%, but there was no statistically significant difference. Furnaz S, et al. in their study found that the most prevalent lifestyle risk factor for CVD was family history of CVD, followed by smoking and higher than normal BMI (13). Our study had similar findings due to smoking, but not with BMI or heredity.

Our study confirmed that medical staffas well as non-medical, had BMI in normal range, though the value varied in the medical staffgroup from 20.5 to 34.0 kg/m^2 and in non-medical group from 18.5 to 34.9 kg/m^2, with a mean value of 24.82 kg/m^2. Contrary to the finding of our study, Kyle R. et al, in a big cross-sectional study based on data from 5 years with 20,103 participants, of which 1570 were health workers, showed that obesity prevalence was high across all medical staff(14). In their study, Obiebi IP, et al. found that only 36.2% of medical staffhad normal BMI (15). Dennis Ko, et al. conducted a study in Ontario, Canada, where he found that physicians had significantly lower baseline rates of hypertension, diabetes, smoking, while having better cholesterol profiles compared with the general population (2). Gosadi IM, et al. published a study in which 234 physicians participated with almost 70% physicians reporting BMI higher than 25 kg/m^2, prevalence of hypertension was 10.3%, type II diabetes 8.5% and dyslipidemia 3.4% (16).

In order to obtain a better and more comprehensive profile of the presence of lifestyle risk factors for CVD in the population of medical workers, it would be necessary to conduct a study with a larger number of participants and add the way of nutrition and the existence of stress, which would process the risk factors more comprehensively.

CONCLUSION

Since medical staff is one important factor in any health strategies employed, they should also set an example by taking care of their own health. Their work includes high-risk environment, shift work, mental as well as physical stress and other lifestyle risk factors for CVD. So, lifestyle measures to reduce the burden of risk factors for CVD should be established among medical staff.

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Reprint request and correspondence:
Slavenka Štraus, MD, PhD
Clinic of Cardiovascular Surgery
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: vstraus@yagoo.com
ORCID: 0000-0002-0912-7636

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Helicobacter Pylori infection - cancer detection: microbiology culture or serology?

Infekcija Helicobacter Pylori - otkrivanje kancerogena: mikrobiološka kultivacija ili serologija?

Amila Mehmedović*[1,4], Daria Bekić[2], Melika Bukvić[3], Haris Kurić[3], Besim Prnjavorac[5]

[1]Clinic of Gastroenterology and Hepatology, Clinical Centre University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[2]Clinical Microbiology, Clinical Centre University of Sarajevo , Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[3] Radiology Clinic, Clinical Centre University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[4]Sarajevo School of Science and Technology, Hrasnička cesta 3a, Ilidža 71210, Bosnia and Herzegovina
[5]Faculty of Pharmacy, University of Sarajevo, Zmaja od Bosne 8, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: infection with Helicobacter pylori is a permanent initiator of the inflammatory reaction, proven promoter of tumour growth for gastric mucosa, I class cancerogen in human gastric carcinoma. The trend towards increasing prevalence of Helicobacter pylori antibiotic resistance may jeopardize the efficacy of most regimens. Microbiological culture of the H. pylori is the useful method able to address therapy. Aim: to analyse the incidence of chronic H. pylori infection in malignant diseases of gastric and colorectal localization, its duration, based on serology and microbiological cultivation. We evaluated the accuracy of culture for detection of H. pylori in a clinical dedicated laboratory.
Materials and methods: a total of 180 patients were divided into three groups depending on the localization of the tumor (gastric tumors; colorectal tumors; control group- subject with no malignancy), and further into subgroups with respect to H. pylori positivity. The subjects were processed clinically, laboratory, endoscopically, microbiologically and with serological determination of H. pylori infection. Microbiological cultivation of H. pylori was determined after taking a biopsy of the gastric mucosa, during proximal endoscopy. Results: the average duration of H. pylori infection, was the longest in the group with gastric tumors (5.24 years), then in the group with tumors of extragastric localization (5.0 years), then in the control group (3 years). Microbiological culture showed sensitivity 96.7%, specificity 100%, and accuracy 97.8%. Positive and negative predictive values were 100% and 94.1%, respectively.
The largest number of subjects in groups with malignant alteration was previously treated with triple therapy, but the success of the treatment was not confirmed. The control group has the largest number of newly discovered H. pylori infected subjects, and has not yet been treated. Analysis of findings of distal endoscopy in extragastric tumors showed: a significantly higher number of patients with sigmoid malignancy, in H. pylori positive subjects, and in H. pylori negative subjects, the localization was the rectum. In relation to the occurrence of gastric cancer, the following factors showed statistical significance in this study: presence of H. pylori (direct and indirect tests), duration of H. pylori infection, positive family history, previous cholecystectomy, smoking, male sex. In relation to the occurrence of colorectal cancers, the following factors showed statistical significance in this paper: IBD, previous cholecystectomy, smoking, duration of H. pylori infection, positive family history, male sex. Conclusion: H. pylori infection represents a risk factor of malignant alteration in gastric mucosa. It is proposed to take this risk factor in to account, for early screening for gastrointestinal tumors, along with others. Microbiological culture of H. pylori is a feasible direct method and provides a good level of diagnostic accuracy in detection and follow -up of treatment of H. pylori eradication.

Keywords: Helicobacter Pylori, microbiological culture, serology, malignant alteration of the digestive tract

SAŽETAK

Uvod: infekcija bakterijom Helicobacter pylori je trajni pokretač upalne reakcije, dokazani promotor rasta tumora želučane sluznice, karcinogen I klase karcinoma želuca. Trend povećanja antibiotske rezistencije Helicobacter pylori, utiče na djelotornost većine terapijskih režima. Mikrobiološka kultivacija H.pylori je korisna direktna metoda koja se može uticati na procjenu terapijske djelotvornosti kao i izbor terapije. Cilj rada je bio analizirati incidenciju hronične H. pylori infekcije njezino trajanje, na temelju seroloških i mikrobioloških kultivacija, kod pacijenta sa malignim bolestima želučane ili kolorektalne lokalizacije, u poređenju sa pacijentima kontrolne skupine. Procijenili smo tačnost mikrobiološke kultivacije za detekciju H. pylori u bioptatu sluznice želuca. Materijali I metode: ukupno 180 bolesnika podijeljeno je u tri skupine ovisno o lokalizaciji tumora (tumori želuca; kolorektalni

tumori; kontrolna skupina - ispitanici bez maligne bolesti), te dalje u podskupine s obzirom na H. pylori pozitivnost. Mikrobiološka kultivacija H. pylori određena je nakon uzimanja biopsije želučane sluznice, tijekom proksimalne endoskopije.
Rezultati: prosječno trajanje H. pylori infekcije bilo je najduže u skupini pacijenata sa tumorima želuca (5,24 godine), zatim u skupini sa tumorima ekstragastrične lokalizacije (5,0 godina), zatim u kontrolnoj skupini (3 godine). Mikrobiološka kultura pokazala je osjetljivost 96,7%, specifičnost 100%, a točnost 97,8%. Pozitivne i negativne prediktivne vrijednosti bile su 100%, odnosno 94,1%. Analiza nalaza distalne endoskopije kod ekstragastričnih tumora pokazala je: značajno veći broj bolesnika s malignim tumorom sigme, kod H. pylori pozitivnih ispitanika, a kod H. pylori negativnih ispitanika lokalizacija je bila rektum. U odnosu na pojavu karcinoma želuca, statistički značajni u ovoj studiji su faktori: prisutnost H. pylori (direktni i indirektni testovi), trajanje infekcije H. pylori, pozitivna porodična anamneza, prethodna holecistektomija, pušenje, muški spol. U odnosu na pojavu kolorektalnog karcinoma, sljedeći faktor su pokazali statističku signifikantnost, u ovom radu: IBD, prethodna kolecistektomija, pušenje, trajanje H. pylori infekcije, pozitivna porodična anamneza, muški spol. Zaključak: infekcija H. pylori predstavlja faktor rizika maligne alteracije želučane sluznice, koji treba uzeti u obzir, među ostalim, za rano otkrivanje gastrointestinalnih tumora. Mikrobiološka kultura H. pylori izvediva je direktna metoda i pruža dobar nuivo dijagnostičke tačnosti u otkrivanju i praćenju liječenja eradikacije H. pylori.

Ključne riječi: Helicobacter Pylori, mikrobiološka kultura, serologija, maligna alteracija probavnog trakta

INTRODUCTION

Helicobacter pylori (H. pylori) induce chronic gastric inflammation and gastric ulcer and may also be a contributory factor in human gastric carcinoma. Besides its natural habitat in the human stomach, other sources of H. pylori and its mode of transmission are unknown. Identification of the reservoirs and routes of infection of H. pylori has been impeded by the difficulty of isolating the pathogen from foods and environmental sources. This is largely attributed to the fastidious nature of H. pylori and its relatively low growth rate, thereby limiting its growth in a competitive environment (1-3).

After a long history of discoveries on the pathology and bacterial colonization of the gastric mucosa starting in the beginning of the last century, the gastroenterologist Barry Marshall and the pathologist Robin Warren, in the 1980's, fulfilled Koch's postulates for the association between gastritis and the human gastric pathogen Helicobacter pylori (4,5). This decisive demonstration substantially changed our views of the microbiology and pathology of the human stomach and resulted in Marshall and Warren receiving the 2005 Nobel Prize in Physiology and Medicine.

This discovery founded the concept that infection with H. pylori can lead to distal gastric adenocarcinoma (1%-2%), and gastric mucosal-associated lymphoid tissue (MALT) lymphoma (<1%) (6,7). These insights not only dramatically improved the management and therapy of gastric diseases but also provided an invaluable key for deeper insights into the pathogenesis of chronic infections.

Since Helicobacter pylori infection is the one of the confirmed carcinogens for gastric malignancy, currently valid guidelines recommend eradication in verified cases.

The trend towards increasing prevalence of Helicobacter pylori antibiotic resistance may jeopardize the efficacy of most regimens. Culture of the bacterium, the useful method able to address therapy is influenced by various factors. Thus, validation of the procedure is fundamental. Most studies have been carried out in microbiological settings, while only few have been conducted in clinical frames (8-10). A big problem is the detection and monitoring of the success of H. pylori eradication in the general population, given that there are no clear strategies in this field in our regions.

AIM

The aim of the study was to analyse the incidence of chronic H. pylori infection in malignant diseases of gastric and colorectal localization, and in control (non-malignant) subjects, its duration, based on serology and microbiological cultivation. We evaluated the accuracy of culture for detection of H. pylori in a clinical dedicated laboratory.

MATERIALS AND METHODS

The study was conducted at the Clinic of Gastroenterology and Hepatology of the Clinical Center University of Sarajevo (CCUS), and special tests and analyses were performed at the Clinical Microbiology, in period of 2015. - 2019.

The study included 180 respondents divided into three groups of 60 respondents, depending on the localization of the tumor process (1-gastric or 2-extragastric, colorectal localization) and a 3-control group (nonmalignant subjects). Further, all groups were divided into two subgroups each, depending on the presence of H. pylori infection. Subgroups A- were H. pylori positive, while subgroups B - were H. pylori negative respondents.

The respondents were processed clinically, laboratory, endoscopically, microbiologically and with serological determination of monitored parameters.

The following data were taken from all patients:

a) • History of the disease - the presence of proven risk factors for the occurrence of malignant alteration in the digestive tract,
- Available medical documentation on diagnosed or excluded malignant disease in the subject, serological tests and microbiological analysis for H. pylori, tumor markers (CEA, CA 19-9, AFP), EHO or CT abdomen, which are not older than three months,
- Available medical documentation on previous treatment (data on drug abuse, especially NSAIDs),
- Available laboratory documentation with the values of the necessary laboratory parameters.

b) Clinical status of the subject
- General clinical status of the patient.

c) Laboratory processing:
- Serological test for H. pylori (IgA and IgG),

d) Microbiological analysis of biopsies of the gastric mucosa:

• Culture of gastric mucosa biopsies obtained during proximal endoscopy (2x corpus mucosa, 2x antrum mucosa) and direct urease test.

Standard biochemical blood analyses were performed in a local laboratory according to standard methods.

Microbiological analysis was determined successively for each patient, after taking a biopsy of the gastric mucosa, during proximal endoscopy.

They were marked as 4 marked biopsy samples (2 from the antrum and 2 from the corpus) and transported in a transport medium for H. pylori or in a sterile container with physiological solution within half an hour in the laboratory.

Under sterile conditions on a sterile petri dish, each biopsy sample was divided into three parts with a sterile scalpel.

The first part of the immersion in liquid urea and with the second technical urea that serves as a positive control in which Proteus was sown (which gives positive urea) was left in the thermostat to incubate at 37°C for 18 to 24 hours. After that, urea was read, as positive or negative.

The second part of the biopsy was spread on a glass slide and stained by Gram, with the last stage of saffron staining being extended for 15 minutes on the preparation before rinsing. Subsequently, the microscopic preparation was looked at under immersion and the morphologically characteristic bacilli of H. pylori were looked for. If they were visible, thwy were recorded as positive microbiological preparation.

The third part of the biopsy was sown on a selective medium for H. pylori (Pylori agar) or on Columbia agar, placed in a pot with an indicator and bags for microaerophilic incubation. The pot was placed to incubate in a thermostat at 37°C for up to 10 days, being opened after 3 to 5 days to monitor growth. If there was growth on the substrates, a preparation was made which was again stained by Gram and then examined under a microscope under immersion (magnification 100x). Colonies were removed from the culture with sterile tissue and sown again in liquid urea. Urea was again incubated in a thermostat at 37° C, from 18 to 24 hours.

If there was a characteristic growth on the media, positive urea and microscopic preparation, a positive result was issued and if there was no growth, the incubation was extended up to 10 days, and in case of growth we repeated the procedure with urea and microscopic preparation, but if there was no growth even then, a negative result was issued.

Based on the microbiological findings, eradication therapy for H. pylori was immediately included, when necessary.

To determine the stage of the malignant disease, proximal, distal endoscopy, pathohistological diagnosis, radiological evaluation, basically the TNM classification was used.

For the group of control subjects, the absence of tumors of the digestive tract was determined based on laboratory findings, proximal and distal endoscopy, EHO of the abdomen and tumor markers CEA, CA19-9, AFP, which the patient had previously obtained, no older than three months. Only respondents who previously had this documentation were included.

Radiological examinations included ultrasound and CT of the abdomen, as part of the assessment of the disease stage.

Ethical statement

The study was approved by the Ethics committee of the Clinical Center University of Sarajevo, and it was conducted according to the Declaration of Helsinki, GCP, GLP protocols and local regulations.

All identification data were masked and permanently protected according to regulations on the protection of identification data. In order to protect personal data, each patient was assigned with an identification number that was used in statistical data processing. Confidentiality of personal data was guaranteed by the researcher, the author of this paper.

The respondents had no economic or any other interest from participation in the study.

Tests to which the respondents were subjected were routine and carried out with the aim of establishing an accurate diagnosis and a better therapeutic approach to the patient.

No patient was included in the study without a previously voluntarily signed informed consent.

Statistical analysis

Upon completion of the examination, statistical processing of the data was carried out and complete statistics on the conducted examination were produced. The results are presented in tabular and graphical form.

The data were statistically evaluated using the MS Excell program, and then processed using the statistical package Statistic for Windows.

The following statistical methods were used:

• Descriptive statistics, variance analysis test (ANOVA test), adapted to the analysis of three or more groups, multivariate analysis. Furthermore, the calculation of the multivariate analysis ranks the parameters according to the degree of relative predictive value for the occurrence of the observed, defined event. After the calculation of the multivariate analysis, a statistical analysis of the most significantly ranked parameters was additionally performed, in order to calculate the existence of statistical significance in the influence of the parameters on the expected outcome and its significance. During the subsequent calculation, it was not allowed to reuse the parameters obtained by the calculation for new mathematical operations of statistical analysis. In order to determine which of the inflammatory parameters had the highest predictive value for the intensity of the process, a multivariate analysis - discriminant method was used.

The interdependence of individual groups of parameters was analysed by the multiple correlation test. The level of significance was $p<0.05$.

RESULTS

A total of 180 respondents were treated, divided into three groups of 60 respondents, depending on the localization of the tumor process (gastric or extragastric, colorectal localization) and a control group - 60 respondents.

Furthermore, all groups were divided into two subgroups each, depending on the presence of H. pylori infection. Subgroups A respondents were H. pylori positive, while subgroups B respondents were H. pylori negative. The results were presented according to the set goals.

The analysis of the age structure showed an average older age in the groups with the presence of a malignant disease, compared to the healthy (non-malignant) subjects. On average, subjects with gastric tumors were older (in years) than subjects with colorectal tumors (60.3 vs. 64.8).

Table I **Basic demographic parameters of the respondents by groups/subgroup SD – Standard deviation.**

Subgroup	Age (years) (SD)
1a	63,40 (10,23)
1b	66,37 (10,45)
2a	59,93 (12,30)
2b	60,80 (13,49)
3a	48,96 (12,53)
3b	45,00 (12,00)

The average duration of H. pylori infection, expressed in years, was the longest in the group with gastric tumors (5.24 years), followed by the group with tumors of extragastric localization (5.0 years), and finally in the control group (3 years), parametric T test, p=0,03 Figure 1.

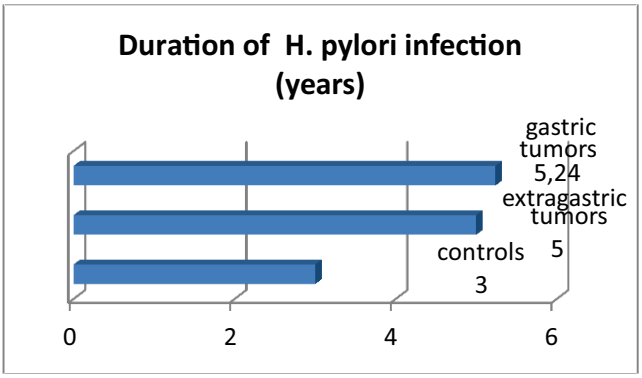

Figure 1 **Duration of H. pylori infection by groups (years).**

Microbiological analysis of biopsies showed that in all cases positive for H. pylori, the urease test was positive. In group 1, four samples were urease positive, culture negative, and in group 2 there were three samples.

Regarding the duration of the known H.pylori infection, the ANOVA test showed significant difference between patients with malignancies and the control group (p= 0.04)but no significant difference between the groups of patients with gastric or extragastric tumours.

In the control group, all were urease positive, culture positive - Figure 2.

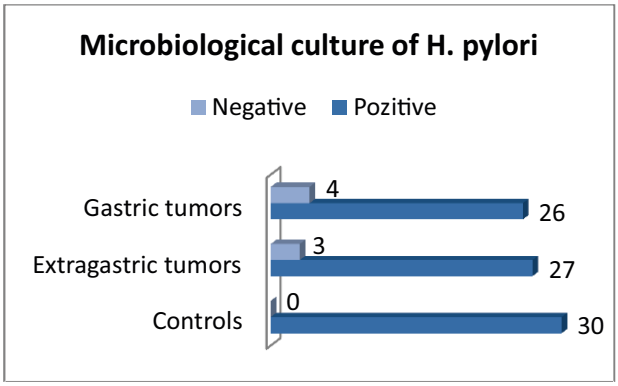

Figure 2 **Microbiologic cultures of H. pylori (No of pts).**

Serological analysis was predominantly IgG positive and IgA positive. In a smaller number of cases, IgG was positive, IgA was negative - Figure 3.

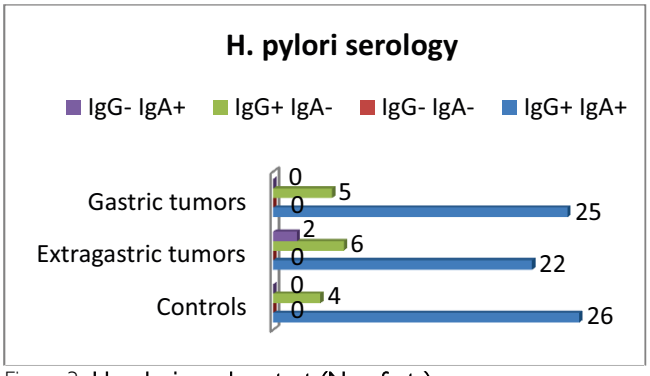

Figure 3 **H. pylori serology test (No of pts).**

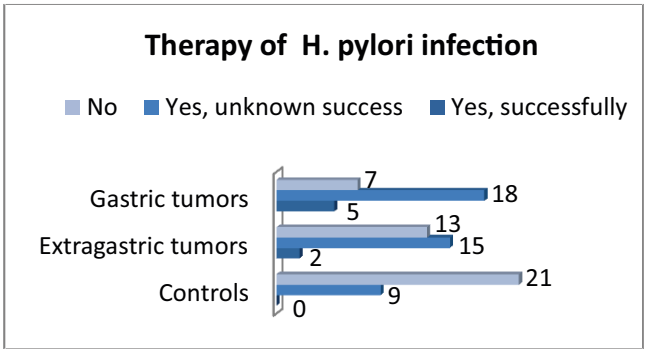

Figure 4 **Therapy of H. pylori (No of pts).**

Figure 4 shows the results of the treatment of H. pylori infection by group. The largest number of respondents in groups 1 and 2 were previously treated with triple therapy, but the success of the treatment was not confirmed. The control group had the largest number of newly discovered H. pylori infected respondents, and it had not yet been treated.

Microbiological culture showed sensitivity of 96.7%, specificity of 100%, and accuracy of 97.8%. Positive and negative predictive values were 100% and 94.1%, respectively (Cohen's kappa).

Analysis of distal endoscopy findings in extragastric tumors showed: a significantly higher number of patients with sigmoid malignancy, in H. pylori positive and in H. pylori negative respondents, the localization was the rectum.

In the statistical analysis, a multivariate analysis test ("Factor analysis" model) was performed and a stratification of significant factors, predictive parameters, was made in relation to H. pylori positivity and the presence of gastric cancer, followed by extragastric cancer. The results of the statistical processing showed that male gender and younger age was statistically significant in connection with H. pylori positivity in the group of respondents with gastric tumors, p=0,04.

In relation to the occurrence of gastric cancer, the following factors showed statistical significance in this study: presence of H. pylori (direct and indirect tests) p=0,04, duration of H. pylori infection (p= 0,04), positive family history (p=0,04), previous cholecystectomy (p= 0,03), smoking(p= 0,04), male sex (p= 0,04).

In relation to the occurrence of colorectal cancers, the following factors showed statistical significance in this study: IBD (p= 0,04), previous cholecystectomy(p=0,04), smoking (p=0,04), duration of H. pylori infection(p=0,04), positive family history=003), male sex (p= 0,03).

DISCUSSION

Cancer is a systemic disease, and prolonged inflammation is a hallmark of cancer (11). Whether this inflammation initiates tumorigenesis or supports tumour growth is context dependent, but ultimately the global immune landscape beyond the tumour becomes significantly altered during tumour progression. Over the last decade, targeting the immune system with immunotherapy has revolutionized cancer therapy. Recent clinical and preclinical studies are beginning to unravel the range of systemic immune perturbations that occur during tumour development.

One of the confirmed carcinogens for gastric malignancy is chronic H. pylori infection.

Considering that this is a chronic, "smoldering" inflammation, the pathophysiology of which has not been fully elucidated even to this day, and that the malignant alteration most often occurs after many years of the presence of bacteria, the immune response of the organism can be seen as a "mirror" of its progression.

The most recent efforts of researchers are towards examining a panel of cytokines and risk factors, with the aim of predicting the risk of malignant diseases of the alimentary canal.

Studies analysed the role of inflammatory processes in the tumor environment, emphasizing the important role of cytokines that promote tumor growth and spread (12-15).

An interesting study by Tong W, et al. who investigated the predictive role of the panel of biomarkers VEGF, ADAM 8, IgG to H. pylori, serum pepsinogen I and pepsinogen II, and concluded that the panel has significance for monitoring gastric cancers, without repeating proximal endoscopy (16). A new term is introduced in oncology - "cytokines", as a pattern of malignant growth monitoring (17).

Research on the influence of chronic inflammation on the development of malignancy has long been known for colorectal cancer. The results of the meta-analysis by Hong SN, et al. confirm that there is an increased number of H. pylori positive subjects in colorectal adenomas (18).

The research shows that, in relation to the occurrence of gastric cancer, the following factors showed statistical significance in this study: presence of H. pylori (culture and serology tests), duration of H. pylori infection, positive family history, previous cholecystectomy, smoking, male sex.

In relation to the occurrence of colorectal cancers, the following factors showed statistical significance in this paper: IBD, previous cholecystectomy, smoking, duration of H. pylori infection, positive family history, male sex.

In recent years, as the resistance rate of H. pylori to clarithromycin has increased, the eradication rate of the existing standard triple therapy has tended to decrease. To overcome this, the treatment period has been extended or non-bismuth quadruple therapy is recommended (19- 22). Microbiological culture enables the determination of antibiograms in selected cases.

CONCLUSION

H. pylori infection represents a risk factor of malignant alteration in gastric mucosa. It is proposed to take this risk factor in to account, for early screening for gastrointestinal tumors, along with others. Microbiological culture of H. pylori is a feasible direct method and provides a good level of diagnostic accuracy in detection and follow-up of H.pylori eradication treatment.

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Reprint requests and correspondence:
Amila Mehmedović, MD, PhD
Clinic of Gastroenterology and Hepatology
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: amila.mehmedovic@sssst.edu.ba
ORCID ID: 0000-0002-3231-2805

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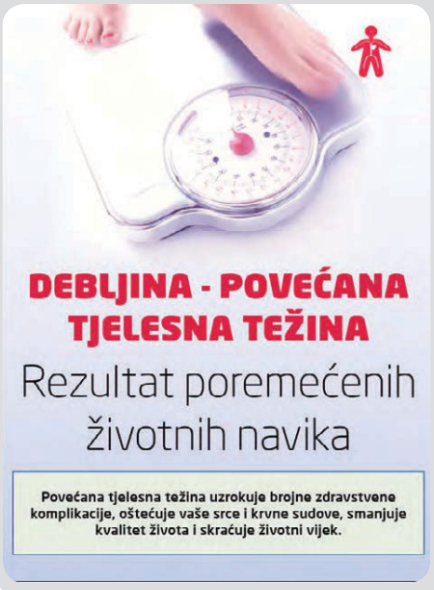
Bosnia and Herzegovina versions of Guidelines for Patients!
Bosanskohercegovaka verzija Vodia za pacijente!



Paraneoplastic encephalitis: case report

Paraneoplastični encephalitis: prikaz slučaja

Elma Milanović[1]*, Binasa Bašić[2], Mirhan Salibašić[3], Edin Hodžić[3], Merima Krušćica[3], Nevena Mahmutbegović[1]

[1]Clinic of Neurology, Clinical Center University of Sarajevo, Bolnička 25, 7000 Sarajevo, Bosnia and Herzegovina
[2]Department of Neurology, Hospital Travnik, Kalibunar bb. 72 270 Travnik, Bosnia and Herzegovina
[3]Clinic of Abdominal Surgery, Clinical Center University of Sarajevo, Bolnička 25,71 000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: paraneoplastic encephalitis is an immune mediated paraneoplastic syndrome mainly related to lung cancer, breast cancer and prostate cancer. Gastrointestinal neoplasms, amoung the, intestinal tumors, have rarely been associated with development of paraneoplastic encephalitis. Case report: we present the case of a 52-year-old male patient with a rare presentation of paraneoplastic encephalitis and underlying intestinal and with subacute cognitive deterioration, and psychiatric symptoms. Serologic test were negative. Brain MRI showed meningeal enhancement with suspicion for pachymeningitis. Onkoneural antibodies were negative, but diagnostic evaluation relieved enteropathy-associated T-cell lymphoma. Conclusion: prompt diagnosis of paraneoplastic encephalitis is extremely important due to the focus of the diagnostic process on the early detection of the previously unknown neoplastic process. The unclear clinical presentation makes the diagnosis sometimes difficult to establish. However, early diagnosis is associated with better prognosis, and possibility to avoid consequential sequelae.

Keywords: paraneoplastic encephalitis, paraneoplastic syndrom, intestinal tumor

SAŽETAK

Uvod: paraneoplastični encefalitis je imunološki posredovan paraneoplastični sindrom koji se uglavnom odnosi na rak pluća, dojke i prostate. Gastrointestinalne neoplazme, među kojima su i crijevni tumori, rijetko su bile povezane s razvojem paraneoplastičnog encefalitisa. Cilj: Prikazujemo slučaj sredovječnog muškarca. Prikaz slučaja: prikazujemo 52-godišnjeg pacijent s rijetkom prezentacijom paraneoplastičnog encefalitisa i tumorom crijeva sa subakutnim kognitivnim pogoršanjem i psihijatrijskim simptomima. Seroloski testovi su bili negativni. MRI mozga pokazao je prebojavanje meningealnih ovojnica sa sumnjom na pahimeningitis. Onkoneuralna antitijela bila su negativna, ali dijagnostička obrada ukazala je na T-stanični limfom povezan s enteropatijom. Zaključak: pravovremena dijagnoza paraneoplastičnog encefalitisa iznimno je važna zbog usmjerenosti dijagnostičkog procesa na rano otkrivanje do sada nepoznatog neoplastičnog procesa. Nejasna klinička slika ponekad otežava postavljanje dijagnoze. Međutim, rana dijagnoza povezana je s boljom prognozom i mogućnošću izbjegavanja posljedičnih sekvela.

Ključne riječi: paraneoplastični encefalitis, paraneoplastični sindrom, tumor crijeva

INTRODUCTION

Paraneoplastic encephalitis (PE) is a rare condition characterized by central nervous system (CNS) dysfunction without direct involvement with tumor cells. Despite the low incidence of occurrence, the significance of this diseases is huge, because very often precede the appearance of malignant tumors, which allows tumors to be detected while still in the early stage, when a significantly higher is the effectiveness of treatment (1). The proposed pathophysiological mechanism is the activation of the immune system response to antigens of tumor cells. Because it is clinically manifested by a whole range of neuropsychiatric symptoms, sometimes is very difficult to make a diagnosis (2).

The diagnosis of PLE is made by excluding other causes of CNS malfunction, such as infections, metastases in brain or metabolic disorders. Among PLE patients, about 50% have lung cancer, 20% testicular tumors and 8% breast cancer; less commonly associated neoplasms are Hodgkin's lymphoma, thymoma or teratoma. Although several reports published in recent decades have shown

the appearance of PLE in different types of cancer, only a few cases are associated with gastrointestinal (GI) neoplasms.

A significant number of these PLE syndromes are caused by secretory products of neuroendocrine cells, mainly peptide hormones that are widely dispersed throughout the lungs, gastrointestinal tract, pancreas, thyroid and adrenal marrow. Further symptoms may be the result of autoantibodies produced against tumor cells that can cross-react with a number of normal cellular constituents.

The prognosis of PLE is poor. It is generally believed that patients with positive antibodies have a worse prognosis than patients in whom no antibodies have been detected. Patients with present antibodies to membrane antigens are thought to have a better prognosis than patients with antibodies to intra-neural antigens (2).

AIM

Our aim was to present a brief overview of neurological symptomatology within paraneoplastic encephalitis in a patient with a tumor of the small intestine.

CASE REPORT

A 52 years old male patient was admitted to Clinic of Neurology due to involuntary movements of the upper, and then the lower extremities which started 5 months before and all accompanied by occasional febrile state up to 39.5 0 C. Further, there was a loss of body weight (8 kg) and night sweats. He was treated with dual antibiotic therapy for 12 days for bicytosis (leukocytosis and thrombocytosis), then referred to neurological examination. During hospitalization at the Neurological Clinic, the clinical picture was complicated with focal epileptic seizures, without generalization, with mild cognitive dysfunction. His neurological examination relieved pronounced involuntary movements on upper extremities; oscillating weakness of both legs. He was unable to stand alone, without help. Cognitive screening was performed: Mini-Mental State Examination (MMSE): 26/30; Montreal Cognitive Assessment (MoCa) 24/30; Adenbrookes - Cognitive Examination ACE-R (80). In laboratory, reactive leukocytosis (WBC) 11.58 x10^9/L (4-10) was recorded, slightly elevated nonspecific inflammation parameter CRP 38.4 mg/L (0-10), and secondary microcytic anemia, erythrocytes (RBC) 4.24 x10^12/L (4.3-5.7) Hemoglobin 105 g/L (138-175) Hematocrit 33% (41-53), Iron 2.9 umol/L (11.6-31.6) with reactive thrombocytosis platelets (PLT) 551 x10^9/L (150-400). In the cerebrospinal fluid (CSF), we observed high proteins 0.5 g/L/ ref/ 0.1-0.4. Complete serological analysis was negative (Toxoplasma gondii, Rubella virus, CMV, HSV, EBV, Treponema pallidum, HIV, WNV, Borelia Burgdorferi, Echinococcus granulosus, Coxiella burneti). Complete immunological tests, including ANA, Anti ds DNA, ENA 6 profile, CIC, AMA, ASMA, c anca, panca, complement, anticardiolipin antibodies were negative, except for serum amyloid which was slightly elevated. Hormonal status OF the thyroid gland was normal. Hepatitis markers, levels of copper in 24 urine, ceruloplasmin and copper in serum were negative. We observed slightly elevated CEA 7.82 ng/mL (ref 0-5 ng/mL, other tumor markers were negative. Serum and CSF antibodies to autoimmune encephalitis (AMPA1, LGI1, NMDA, AMPA2, CASPR2, GABARB1/B2) were negative. Paraneoplastic serum antibodies were also negative. Brain MRI showed possible localized pachymeningitis.

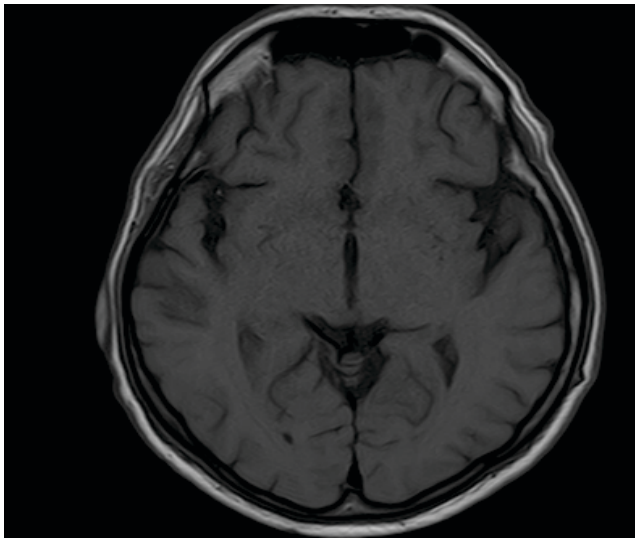


Figure 1 **Brain MRI (T1 weighted image) revealed localized pachymengeal staining.**

We performed series of EEG registrations describing elevated electrocortical epileptic activity over anterior fronto-temporal regions, and non-rhythmic, nonspecific hypersynchrony activity with interposed individual sharp waves and spike-wave complexes. Psychological exploration relieved cognitive decline in the field of memory (dissociation between verbal and visual modalities), learning (impaired processing of information), visuo-constructive and visual features. Abdominal CT scan relieved a neoplasm of the small intestine.

The course of the disease was complicated by Clostridium difficile infection, why we decided against application of pulse corticosteroid therapy. In the in the meantime, an oncologist and an abdominal surgeon were consulted, a medial laparotomy was done with resection of the small intestine with radix mesenteric and concomitant enlarged lymph nodes. Patohystological analysis relaved enteropathy-associated T-cell lymphoma (EATL).

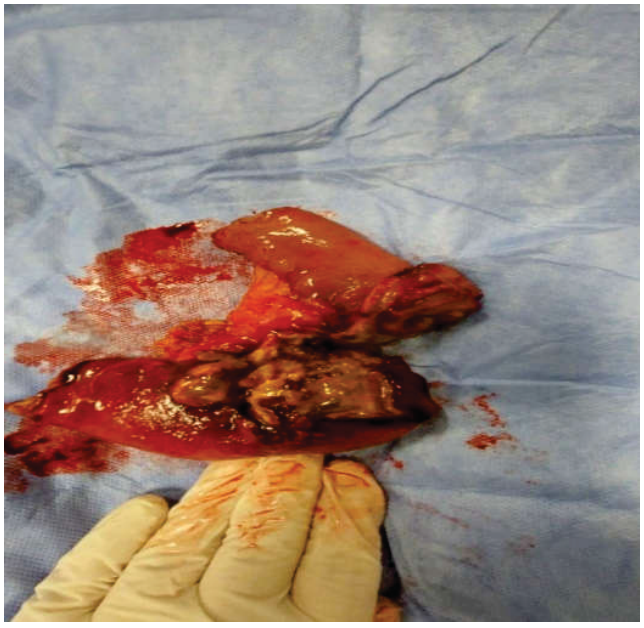


Figure 2 **Resected small intestines with expulsed tumor.**

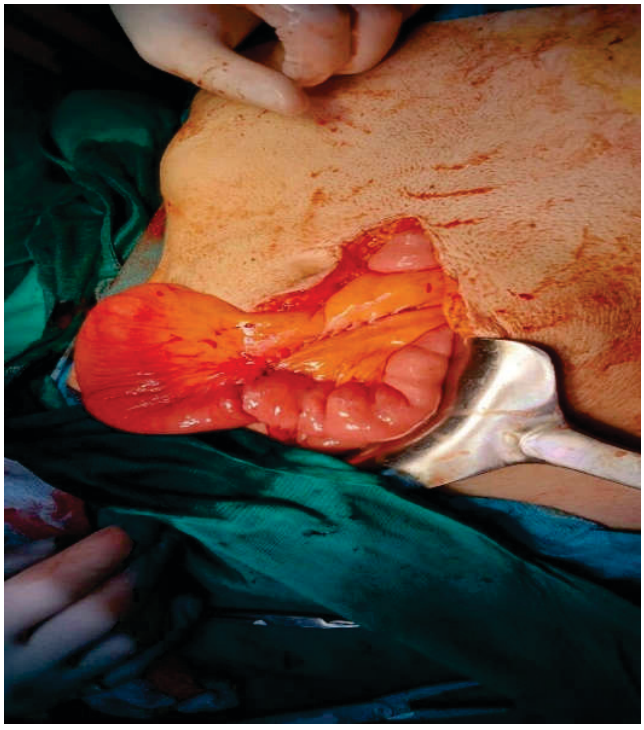


Figure 3 **Condition after establishing the continuity of the digestive tube by end-to-end anastomosis.**

DISCUSSION

Paraneoplastic encephalitis is a varient of paraneoplastic sydrom, immune mediated due to the activation of the immune response to tumor cell antigens. Although, low prevalence of this condition has been described, the diagnostic significance of identifying the etiology of the symptoms, which leads to the early discovery of the tumor, is exceptional (2,3).

Most often, patient present with neurological and psychiatric symptoms, including alteration of consciousness, cognitive declining, hallucinations, disorientation, extremites weakness and epileptic seasures (4-8). In up to 70% of cases, these symptoms are present much prior to oncological diagnosis (9).

While several previous reports reported an association of PLE with small-cell lung cancer, testicular tumors, and breast cancer, only few authors described PLE in gastrointestinal tumors (5, 10). Hooda K, et al. presented a case of PLE in patient with rectal adenocarcinoma (10). Jia XT, et al. described a case of limbic encephalitis in patient with gastric cancer (11). Several authors described cases of PLE in patient with colon cancer; however, we performed an extensive literature search and did not find any reported case of PLE in intestinal neoplasms (8). Most common presentations of intestinal cancers are occult gastrointestinal hemorrhage, abdominal pain and biliary obstruction. Frequently, they are diagnosed incidentally due to long asymptomatic period and mild clinical symptoms (12,13). Enteropathy-associated T-cell lymphoma (EATL) is a rare intestinal lymphoma, which normally affects older people, over the age of 60 years, often with celiac disease. Dominant clinical presentations include abdominal pain, weight loss, diarrhoea, fatigue and an itchy rash (14). Paraneoplastic manifestations of EATL in people have not been described; however several authors reported paraneoplastic hypereosinophilia in animals diagnosed with Intestinal T-cell lymphoma (15-17).

Extremely helpful in diagnosing paraneoplastic encephalitis is detection of paraneoplastic autoimmune antibodies. Anti-Hu antibodies are the most common paraneoplastic antibodies and are found in approximately 50% of patients. Other antineural antibodies associated with paraneoplastic limbic encephalitis are anti-Mu2, anti-CV2, anti-amphiphysin, and anti-PCA2 antibodies. On the other hand, approximately 40% of patients with PE develop relevant immune responses that are not identified by currently available commercial tests (3).

In our case report, paraneoplastic antibodies in the serum, as well as antibodies to autoimmune encephalitis were not detected. Patient presented with subacute cognitive deterioration, and psychiatric symptoms-core features of proposed diagnostic criteria for PE (18). An MRI of the brain showed meningeal enhancement with suspicion for pachymeningitis. Typical radiological findings in PE include range of presentations from T2 hyperintensity and involving of the limbic system to atypical patterns (19). Therefore, the patient, with suspicion of PE, requires an extensive diagnostic evaluation. Diagnosis relay on typical subacute clinical presentation, limbic system abnormalities on MR imaging, EEG showing epileptic or slow-wave activity in the temporal lobes or CSF pleocytosis, and reasonable exclusion of other etiologies (20). It is generally believed that patients with positive antibodies have a worse prognosis than patients in which have not been proven antibodies. Research conducted by Gultekin SH, et al. (4) indicates that the 64% of patients with PLE who did not have positive antibodies experienced

significant improvement of neurological symptomatology in relation to patients with positive antibodies.

There are two proposed therapeutic approach options: identification and removal of the underlying tumor or immunosuppression of the immune system with steroids, immunoglobulins, and plasma exchange.

In our case, the patient was treated surgically and due to the ongoing infection of Clostridium difficile, pulse corticosteroid therapy was not applied. There have been reports of remission in psychiatric and neurological manifestations following treatment of the underlying tumor, however further monitoring of this patient is required.

CONCLUSION

Prompt diagnosis of paraneoplastic encephalitis is extremely important due to the focus of the diagnostic process on the early detection of the previously unknown neoplastic process. The unclear clinical presentation makes the diagnosis sometimes difficult to establish. However, early diagnosis is associated with better prognosis, and possibility to avoid consequential sequelae.

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Reprint requests and correspondence:
Elma Milanović, MD
Clinic of Neurology
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: milanelllllll@gmail.com
ORCID ID: 0009-0007-7594-0266

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Hypersensitivity pneumonitis after COVID-19 infection

Hipersenzitivni pneumonitis nakon COVID-19 infekcije

Belma Paralija[1*], Selma Kadić[1], Kerima Maglajlija-Homoraš[2]

[1]Clinic of Lung Diseases and Tuberculosis, Clinical Centre University of Sarajevo, Bardakčije 90, 71000 Sarajevo, Bosnia and Herzegovina
[2]Public Institution Health Center of Sarajevo Canton, Vrazova 11, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: hypersensitivity pneumonitis (extrinsic allergic alveolitis) is a complex syndrome with different intensity of clinical presentation and nature of origin. There is an acute, subacute and chronic form. Aim: we present a case of hypersensitivity pneumonitis in a 53-year-old woman admitted to the Clinic of Lung Diseases and Tuberculosis of the Clinical Center University of Sarajevo due to dyspnea and cough as well as chest CT scan verified diffuse ground glass opacities. Case report: dyspnea and cough persist after recovering from COVID-19 infection in the previous year. Diffuse areas of ground glass opacities and thickening of the interlobular septa were seen on the chest CT scan, which was unchanged compared to the CT scan performed during the COVID-19 infection. Atypical resection of the right 6th lung segment was pathohistologically proven to be subacute hypersensitivity pneumonitis. Prednisone treatment was started with a successive dose reduction, and the patient was also monitored radiologically. Results: the radiological regression of the previously described changes was confirmed six months after corticosteroid treatment onset. Conclusion: all changes in the lung parenchyma with slow radiological regression should be accurately diagnosed pathohistologically after lung biopsy.

Keywords: hypersensitivity pneumonitis, chest CT scan, pathohistological diagnosis

SAŽETAK

Uvod: hipersenzitivni pneumonitis (extrinsic alergijski alveolitis) je kompleksan sindrom sa različitim intenzitetom kliničke prezentacije i prirode porijekla. Razlikujemo akutni, subakutni i hronični oblik. Cilj: prezentiraćemo slučaj hipersenzitivnog pneumonitisa kod 53.-godišnje žene primljene na Kliniku za plućne bolesti, Klinički Centar Univerziteta u Sarajevu zbog dispnee i kašlja, kao i verificiranih difuznih sjena tipa mliječnog stakla na CT-u grudnih organa. Prikaz slučaja: dispnea i kašalj su perzistirali nakon oporavka od COVID-19 infekcije prisutne u prethodnoj godini. Na CT skenu su se vidjele difuzne sjene tipa mliječnog stakla, kao i zadebljanje interlobularnih septi, što je bilo bez promjena u poređenju sa CT skenom urađenim u toku COVID-19 infekcije. Atipičnoma resekcijom 6.-og segmenta desno patohistološki je dokazan subakutni hipersenzitivni pneumonitis. Terapija prednisonom je započeta uz sukcesivno smanjenje doze, a pacijentica je praćena radiološki. Rezultati: Radiološka regresija prethodno opisanih promjena je utvrđena šest mjeseci nakon započinjanja kortikosteroidne terapije. Zaključak: sve promjene u plućnom parenhimu sa sporom radiološkom regresijom bi trebale biti decidno dijagnosticirane patohistološki plućnom biopsijom.

Ključne riječi: hipersenzitivni pneumonitis, CT grudnih organa, patohistološka dijagnoza

INTRODUCTION

Hypersensitivity pneumonitis (HP) is one of the most common interstitial lung diseases (ILD), that presents unique challenges for a confident diagnosis and limited therapeutic options. The disease is triggered by exposure to a wide variety of inciting antigens in susceptible individuals which results in T-cell hyperactivation and bronchioloalveolar inflammation (1).

There is an acute, subacute and chronic form, which depends on the frequency, duration and intensity of exposure and the duration of the disease (2). The diagnosis of HP requires a combination of medical history, clinical manifestations, radiological findings, pulmonary function, bronchoalveolar lavage (BAL) findings, and histopathological characteristics (3).

The most common antigens are organic dust of grain origin, hay, spores of actinomycetes and fungi, tree bark, and proteins of animal origin found in serum, feces or feathers of birds. Depending on the inhaled agent, farmer's lung, poultry farmer's lung, and ventilation pneumonitis are most commonly encountered (2,3).

CASE REPORT

We present a 53-year-old woman diagnosed with hypersensitivity pneumonitis, which was proved after recovering from a COVID-19 infection with the persistence of respiratory symptoms for a year after the acute phase of the COVID-19

infection, as well as persistent lung parenchymal changes on chest CT scan.

A little over a year ago, the patient suffered from COVID-19 infection. Due to the severity of the symptoms and respiratory insufficiency, she was treated at the Infectious Diseases Clinic of the Clinical Centre University of Sarajevo.

The onset of COVID-19 illness was sudden with fever and chills (in 2021). As part of the diagnostic workup during the COVID-19 infection, chest X-ray and then a chest CT scan were performed. Irregular, diffuse patchy shadows were seen bilaterally on chest X-ray, which were consistent with inflammatory infiltrates in COVID-19 infection (Figure 1). Ground glass opacities (GGO) and thickening of the interlobular septa in both lung wings were observed on the chest CT scan images taken (Figure 2).

Figure 1 **Chest X-ray in COVID-19 illness**

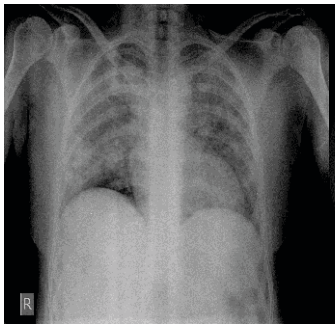
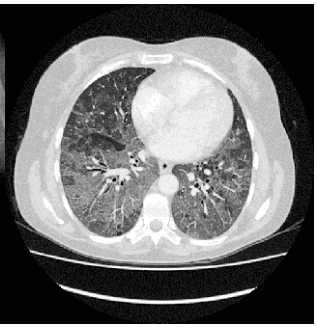


Figure 2 **Chest CT scan in COVID-19.**



Due to the COVID-19 infection, it was assumed that the initial development of acute respiratory distress syndrome (ARDS) was part of the symptoms of the infection at that time.

After the improvement of the symptoms, the patient was discharged from the hospital and later monitored with follow-up of chest radiographs. Respiratory symptoms such as cough, difficulty breathing, fatigue were still present in the following period and were understood as a consequence of the COVID-19 infection. Inhalers were prescribed, to which the patient had some improvement, but still had difficulty breathing and dry cough.

At one point, respiratory symptoms deteriorated and the patient was admitted to the Clinic of Lung Diseases and Tuberculosis of the Clinical Centre of University Sarajevo. The patient provided information that she was engaged in agriculture and lived and worked in the countryside. She was in contact with animals and hay, but had never had respiratory symptoms before COVID-19 infection. No previous allergies were notified. She had had some joint problems before and frequent visits to the doctor due to pain and used therapy for high blood pressure since she had COVID-19 infection.

On admission, the patient was conscious, well oriented, eupnoic at rest, visible mucous membranes and skin of a normal colour, no fever, but with difficulty breathing and rare dry cough. By auscultation bilateral basal inspiratory crackles. Peripheral arterial blood saturation measured by pulse oximeter at room air was 80%. Blood pressure 110/60 mm Hg. In the initial laboratory findings, a slightly elevated CRP was recorded and other laboratory findings normal. Immunological tests were performed, in which elevated IgE and Anti-streptolysin-O titre were recorded. Microbiological analysis of sputum showed normal results. Sputum smear and culture for acid fast bacilli were negative.

Chest radiograph showed bilateral, basal, more laterocostal patchy shadows in the lung parenchyma (Figure 3). Comparing this chest radiograph to the previous one, the same is in slight progression.

Due to the progression of the shadows on the current chest X-ray the patient is referred for a chest CT scan for a more detailed analysis. A comparison was made with the previous chest CT scan (performed a year ago-when suffered from the COVID-19) and it still showed a significantly enlarged pair of lymph nodes in the mediastinum and right hilus and a borderline left hilar lymph node without significant changes. Diffuse zones of the ground glass opacification and thickening of the interlobular septa in both lung wings were still similar in distribution and appearance as on the chest CT scan performed a year ago and still open etiologies (radiological differential diagnosis of shadows as followed: interstitial lung diseases with the development of ARDS, pulmonary alveolar proteinosis, hypersensitivity pneumonitis, systemic connective tissue diseases with pulmonary manifestation atypical bacterial and viral pneumonia, diffuse alveolar hemorrhage (Figure 4).

Figure 3 **Chest radiograph (a year after COVID-19).**

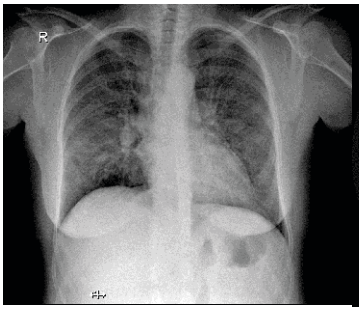
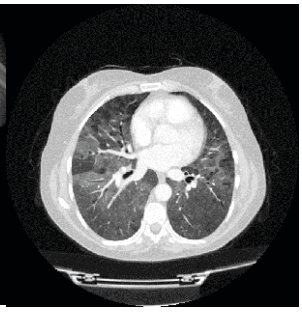


Figure 4 **Chest CT scan (a year after COVID-19).**



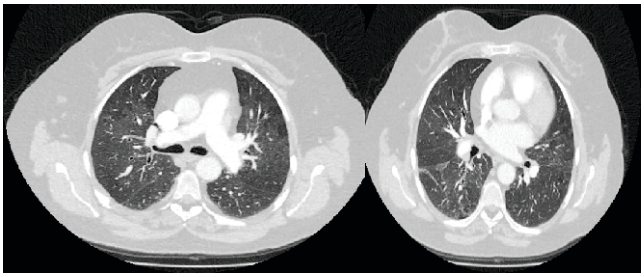
Due to the changes described on the chest CT scan, which were without significant changes compared to the previous one, the patient underwent bronchoscopy procedure. However, due to the patient's non-cooperation (removal of the tube) on two occasions during bronchoscopy, this was abandoned, and the patient's medical history was presented at a multidisciplinary consilium, when an open lung biopsy was indicated at the Clinic of Thoracic Surgery of the CCUS in order to establish an accurate pathohistological diagnosis and etiological clarification of pulmonary infiltrates. The patient underwent lung surgery, and the biopsy samples were sent for pathohistological analysis. Atypical resection of the right 6th lung segment was pathohistologically proven to be subacute hypersensitivity pneumonitis. Pathohistological examination proved subacute hypersensitivity pneumonitis.

Microscopically, fragments of the lung parenchyma with slightly disturbed architecture were visible. In places in the alveoli and focally in the interstitium, histiocytes (CD68+) are seen individually and in small aggregates. Focally present lymphocytic infiltrate in the interstitium with localized formation of aggregates, predominantly located peribronchiolar. Subpleural alveolar spaces filled with eosinophilic homogeneous content (edema) and hemolyzed erythrocytes. Immunohistochemically lymphocytes are: LCA(+), Cd20 (+/-), Bcl2(+/-), Cd3(+/-), Cd23(-), among which individual and in groups histiocytes (CD68+, Cd1a(-), langerin(-) are seen.

We conclude that the cause of our patient's illness was exposure to straw and proteins of animal origin, and that the trigger was the COVID-19 infection a year and half ago. Corticosteroid therapy was started with a successive dose reduction, after which an initial radiological regression occurred. An initial regression were achieved in terms of GGO and thickening of the interlobular septa in both lung wings, as well as regression of hilar and mediastinal lymphadenopathy, on the follow up chest CT scan (six months after starting corticosteroid treatment) (Figure 6,6a).

Figure 6 **Chest CT scan (6 months after corticosteroid treatment onset).**

Figure 6a **Chest CT scan (6 months after corticosteroid treatment onset).**



Other performed diagnostic procedures

Spiroplethysmography and diffusion lung capacity (DLCO) were performed five months after the COVID-19 infection. Ventilatory disturbances of the obstructive type were recorded, as well as a slight decrease in DLCO. Repeated spiroplethysmography and DLCO after one year were without significant deviations. In laboratory findings, slightly elevated inflammatory parameters were recorded, but other parameters were in reference values. At the follow-up examination, the patient reported improvement of respiratory symptoms regarding its reduced intensity. She reported that she had reduced her contact with animals, hay, and the barn. It was not possible to completely isolate herself from the previously mentioned potential antigens, but she usually used a protective mask when working on the farm.

DISCUSSION

In the guideline of the American Thoracic Society, the Japanese Respiratory Society and the Latin American Thoracic Association (ATS/JRS/ALAT) (2020), hypersensitivity pneumonitis was categorized into a fibrous and non-fibrous phenotype depending on the presence and absence of fibrous changes on imaging tests or histopathological analysis (2).

Symptoms of hypersensitivity pneumonitis, regardless of whether it is of the fibrotic or non-fibrous type, include cough and dyspnea, weight loss, and weakness. They can appear acutely (days to weeks), insidiously (months to years) or as recurrent episodes (2). Establishing a diagnosis involves a detailed anamnesis and physical examination of the patient, including information on the conditions of the working environment, then radiological examinations (chest X-ray and CT scan), examination of lung functions, bronchoscopy with bronchoalveolar lavage, and lung biopsy. Physical examination may reveal tachypnea, focal or diffus e crackles, mid-inspiratory crackles. Wheezing is very rarely present. Clubbing fingers are usually associated with more advanced disease (2).Treatment includes short-term administration of corticosteroids, and avoidance of agents thought to cause hypersensitivity pneumonitis. For some patients with HP, abnormal high resolution CT (HRCT) findings, such as the lesions in the lungs, can be absorbed on their own, which is an important clue in the diagnosis of the disease (4).

Interstitial lung diseases (ILD) often represent diagnostic challenges even to expert clinicians. Recent studies emphasized that additional investigations (including surgical biopsy) are indicated in patients with interstitial diseases in whom the diagnosis remains unclear after initial assessment (5). The patient from our case report underwent atypical lung resection after chest CT scan which was almost the same as the previous one (a year ago). The results of the Multicentric HP Study (2003.) indicated that a simple clinical prediction rule may guide clinical practice by providing estimates of the probability of acute, subacute, or chronic progressive HP from noninvasive testing. For instance, in a farmer presenting with recurrent episodes of respiratory symptoms and inspiratory crackles and testing positive for the corresponding precipitating antibodies, the probability of HP would be 81%. Another patient presenting with progressive dyspnea and inspiratory crackles as the only criteria of HP would have a probability of HP of less than 1% (6).

It is well known that patients with chronic lung disease are at risk of developing severe COVID-19 infection, and are likely to have poor outcomes. However, there is a little data available on the progression of interstitial lung disease (ILD) after severe COVID-19 infection, or COVID-19 as a trigger to ILDs or HP. The clinical presentation of severe Covid-19 is similar to that of severe HP (1). In both diseases, cytokine storms, macrophage activation, thrombosis, fibrosis and ARDS are observed, often with a fatal outcome (7). Additionally, influenza virus antigens and coronavirus antigens are frequently detected in bronchoalveolar lavage fluid and lung tissue from HP patients, suggesting that viral antigens can induce HP and that the virus plays an important role as a trigger for disease onset (8,9).

Our patient was working on the farm for a long time and was having contact with hay and domestic animals almost all her life and she had not had any respiratory symptoms, neither myalgias nor headaches until she got the COVID-19 infection. Unfortunately, bronchoscopy was not performed due to the patient's non-cooperation.

Pathohistological examination in our patient revealed subacute form of hypersensitivity pneumonitis which is often without fibrosis on chest CT scans according to Walters, at al. (10). Our patient's first and follow-up CT scans showed interstitial lung disease without developed fibrosis. Walters GI, et al (10) also report in their study that older women suffer from HP more often. Fibrosis on CT scans is associated with a chronic presentation, older age, less pronounced symptoms and less mosaic attenuation on CT scan (10).

Acute or subacute hypersensitivity pneumonitis is treated with corticosteroids, prednisone 60 mg orally once a day for 1 to 2 weeks, then tapered over the next 2 to 4 weeks to 20 mg once a day, followed by weekly decrements of 2.5 mg until the drug is stopped. This regimen relieves initial symptoms but does not appear to alter long-term outcome. Treatment of chronic hypersensitivity pneumonitis is usually with longer courses of

prednisone 30 to 40 mg orally once a day with tapering dependent on clinical response. Some patients require corticosteroid-sparing agents (e.g. mycophenolate, azathioprine) for long-term treatment. The most important aspect of long-term management of hypersensitivity pneumonitis is avoidance of exposure to antigens (11).

Our patient was initially treated with Prednizone 30 mg divided into two daily doses, with lowering the dose monthly depending on clinical response. Satisfactory regression of lung changes and significant clinical improvement were achieved after six months of treatment. It was impossible for our patient to completely isolate herself from potential antigens, but she was advised to at least wear a face mask when working on the farm.

CONCLUSION

HP is a complex clinical problem, and there are substantial gaps in knowledge of pathogenesis. The patient presented in our paper is a rare case of hypersensitivity pneumonitis proven by lung biopsy. Considering the persistence of respiratory symptoms and the slow radiological regression of the changes, a complete diagnostic work-up and an open lung biopsy were required in order to get an accurate pathohistological diagnosis. Based on the foregoing, it could be concluded that all changes with slow radiological regression in the lung parenchyma require pathohistological analysis. As physicians we should be aware that SARS-Cov-2 could potentially act simultaneously as a trigger and substrate for hypersensitivity pneumonitis and other interstial lung diseases due to very similar patophysiology and clinical presentation.

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Reprint requests and correspondence:
Belma Paralija MD, PhD
Clinic of Lung Diseases and Tuberculosis
Clinical Center University of Sarajevo
Bardakčije 90, 71000 Sarajevo
Bosnia and Herzegovina
Email: paralijabelma@gmail.com
ORCID ID: 0000-0001-7556-671X

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Primary cutaneous anaplastic large-cell lymphoma: a case report

Primarni anaplastični velikostanični limfom kože: prikaz slučaja

Nina Čamdžić[1*], Dževad Durmišević[2], Selma Poparić[3], Suada Kuskunović-Vlahovljak[1]

[1]Department of Pathology, Faculty of Medicine, University of Sarajevo, Čekaluša 90, 71000 Sarajevo, Bosnia and Herzegovina
[2]Department of Pathology, Cantonal Hospital "Dr. Irfan Ljubijankić", Darivalaca krvi 67, 77000 Bihać, Bosnia and Herzegovina
[3]Department of Dermatovenerology, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is a CD30 positive T-cell neoplasm that presents with no evidence of extracutaneous disease at the time of diagnosis. Aim: to report a case of PC-ALCL in older male patient with plaque-like solitary lesion on the skin of right hip. Case report: A 74-year-old male presented with a six-month history of asymptomatic poorly circumscribed plaque-like skin lesion. Histology sections revealed diffuse dermal and subcutaneous infiltrates of predominantly large anaplastic tumour cells. Immunohistochemistry showed LCA, vimentin and CD30 positivity of more than 75% of neoplastic cells, together with CD3, CD5, focal CD2 and CD15 positivity. There was no evidence of disseminated disease after detailed body scan. Conclusion: although PC-ALCL is a second most common T-cell clonal neoplasm of the skin, for definite diagnosis requires high clinical suspicion together with correlation of histology with clinical findings.

Keywords: Primary cutaneous anaplastic large-cell lymphoma, T-cell lymphoma, CD30 positive lymphoma

SAŽETAK

Uvod: primarni anaplastični velikostanični limfom kože je CD30 pozitivna T-stanična neoplazma koje u vrijeme postavljanja dijagnoze nema ekstrakutane manifestacije. Cilj: prikazati slučaj starijeg pacijenta sa lezijom koja nalikuje na plak u području kože desnog kuka.Prikaz slučaja: pacijent starosti 74 godine sa šestomjesečnom historijom asimptomatske, slabo definirane lezije poput plaka na koži desnog kuka. Histološkim pregledeom se utvrdi difuzni dermalni i subkutani infiltrat pretežno velikih anaplastičnih tumorskih stanica koje pokažu LCA, vimentin, te CD30 pozitivnost u više od 75% tumorskih stanica. Neoplastične stanice pokažu i CD3, CD5, te fokalnu CD2 i CD15 pozitivnost. Pacijentu nakon detaljnog pregleda cijelog tijela slikovnim metodama nije otkrivena diseminirana bolest. Zaključak: iako je primarni anaplastični velikostanični limfom kože druga najčešća T-stanična klonalna neoplazma kože, za definitivnu dijagnozu zahtijeva visok nivo sumnje kliničara, kao i korelaciju patohistološkog nalaza sa kliničkim nalazima.

Ključne riječi: primarni anaplastični velikostanični limfom kože, T-stanični limfom, CD30 pozitivni limfom

INTRODUCTION

Primary cutaneous lymphomas comprise heterogeneous group of T-cell, B-cell and natural killers cell (NK) neoplasm. Primary anaplastic large cell lymphoma (PC-ALCL) is a T-cell neoplasm that presents in the skin with no evidence of extracutaneous disease at the time of diagnosis (1). The adequate diagnosis requires high clinical suspicion and correlation of histology with clinical findings, since it can overlap not only clinically, but also histologically with other lymphoid lesions (1,2). We report the case of elderly male with plaque-like appearance of solitary skin lesion.

AIM

The aim od this paper was to report a case of PC-ALCL in older male patient with plaque-like solitary lesion on the skin of right hip.

CASE REPORT

A 74-year-old male presented with a six-month history of asymptomatic skin lesion on his right hip. The lesion was plaque-like, poorly circumscribed, skin coloured. The rest of the skin

examination was unremarkable. Routine blood parameters were normal. Surgical excision was conducted.

On gross examination, the lesion measured 5,5x3x2 cm, infiltrating the skin and subcutaneous fat tissue. Histopathology revealed diffuse dermal and subcutaneous infiltrates with moderately cohesive sheets of predominantly large anaplastic tumour cells with round to irregularly shaped nuclei and prominent eosinophilic nucleoli. Some cells showed typical horseshoe-shaped or polylobated nuclei. The epidermotropism was not observed. The background consisted of variable amount of lymphocytes, histiocytes and eosinophils. Immunohistochemistry showed strong and diffuse LCA, vimentin and CD30 positivity of more than 75% of neoplastic cells, together with CD3, CD5, focal CD2 and CD15 positivity. CD7, CD8, EMA and ALK were negative (Figure 1.). Other markers as AE1/AE3, PSA, PLAP, SMA, Desmin, S100 and CD34 were negative and conducted in first-line panel to exclude tumours with similar morphology but of different origin.

The patient was referred to haematology and imaging analysis. CT scan of chest, abdomen and pelvis showed no signs of infiltration of adjacent structures. The ultrasound of inguinal region showed two reactive lymph nodes without evidence of metastatic disease.

The patient is currently on follow-up, without evidence of systemic disease for more than six months.

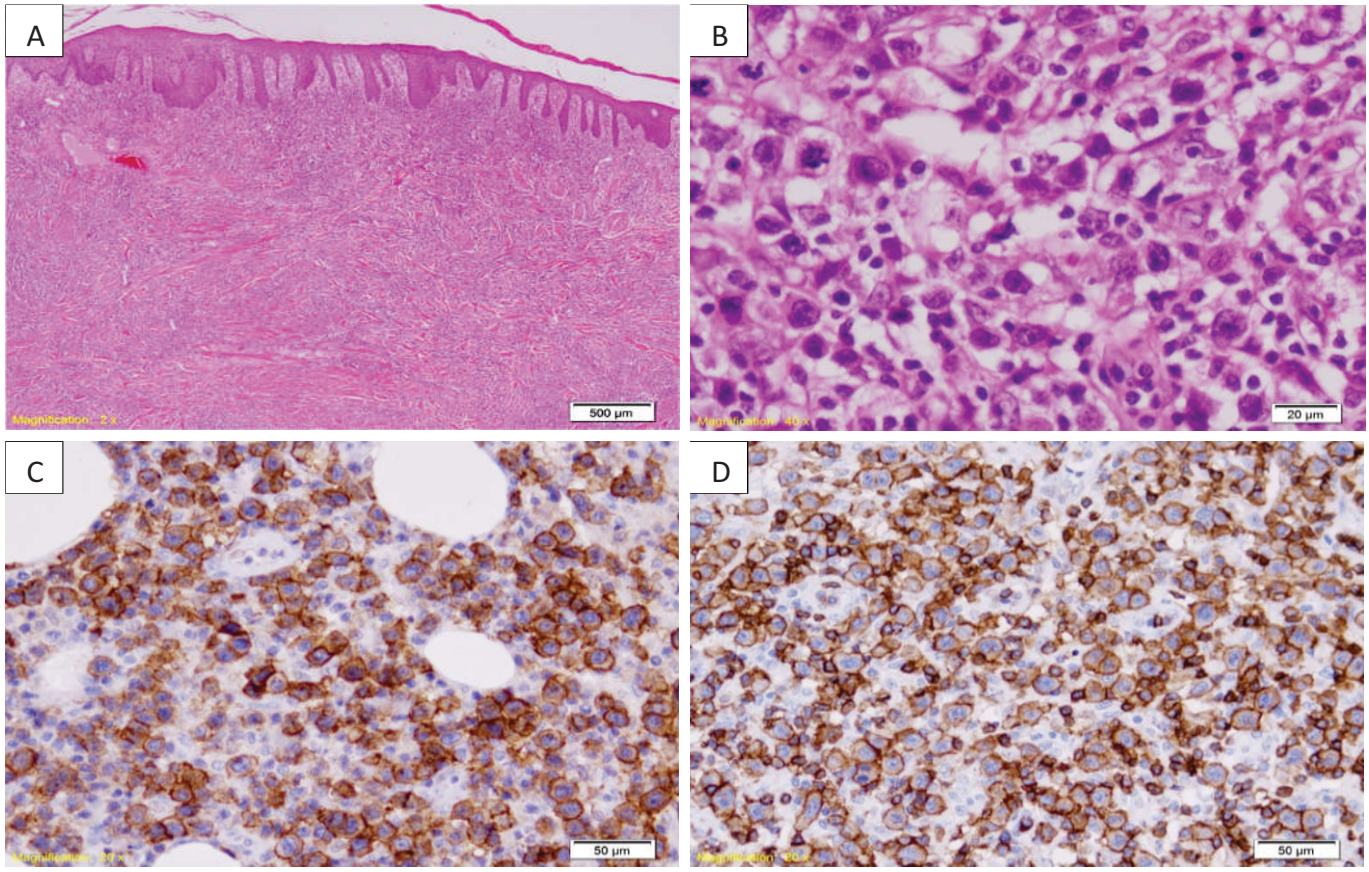

Figure 1 **Anaplastic large cell lymphoma of the skin presenting as diffuse dermal infiltrates of predominantly large anaplastic tumour cells with round to irregularly shaped nuclei and prominent eosinophilic nucleoli: A) (HE, x20); B) (HE, x400). Tumour cells showing CD30 and CD5 positivity: C and D (x200).**

DISCUSSION

Although the skin is the second most common site of extranodal Non-Hodgkin lymphoma (NHL) (3), these neoplasms present rare and heterogeneous group of skin malignancies whose true incidence varies in different parts of the world (4), accounting for approximately 19% of all extranodal NHL (3). According to latest research, cutaneous lymphomas show similar prevalence in both Europe and the USA of around 0.90/100 000 population (5).

The median age at the time of diagnosis is 60 years, with slight male predominance (6). PC- ALCL usually presents as asymptomatic solitary nodule or multifocal papules and nodules that may progress or regress over time (2). In case of our patient, it presented as poorly defined plaque-like lesion on the skin of the right hip. Although localization of lower extremities (6,7), as well as age over 60 years, are considered poor prognostic factors (8) our patient did not experienced progression of skin lesions over six-month period. Two reactively changed lymph nodes of inguinal region were observed, but involvement of the regional lymph nodes does not impact the prognosis nor necessarily means disseminated disease (8). The clinical course of PC-ALCL is predominantly indolent, unlike the course of the systemic forms of anaplastic large cell lymphomas (9).

PCALCL is a T-cell neoplasm characterized by the presence of more than 75% of CD30 positive neoplastic cells with anaplastic, pleomorphic or immunoblastic morphology (10). According to 2016 World Health Organization (WHO) classification, there are four distinct subtypes of anaplastic large cell lymphoma (ALCL): ALK (+), ALK (–), primary cutaneous and breast implant-associated types (11). PC-ALCL can morphologically mimic ALCL together with strong CD30 positivity, but is typically ALK and EMA negative (12).

Classification based solely on histology is not always possible since it has overlapping morphology with systemic ALCL and many T-cell cutaneous lymphomas. It is mainly important do differentiate PC-ALCL from lymphomatoid papulosis, Mycosis fungoides, systemic ALK negative ALCL with cutaneous involvement and CD30 positive reactive conditions (12).

CONCLUSION

Although PC-ALCL is a second most common T-cell clonal neoplasm of the skin after Mycosis fungoides, definite diagnosis requires high clinical suspicion together with correlation of histology with clinical findings. The localization of skin lesions can be an important, as well as detailed body scan to exclude disseminated form of the disease.

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Reprint requests and correspondence:
Nina Čamdžić, MD
Department of Pathology,
Faculty of Medicine, University of Sarajevo,
Čekaluša 90, 71000 Sarajevo
Bosnia and Herzegovina;
Email: nina.camdzic@mf.unsa.ba
ORCID ID: 0000-0002-0327-1151

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