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Formerly Çağdaş Tıp Dergisi

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Book

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Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

An organization as an author

The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

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The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

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JOURNAL OF CONTEMPORARY MEDICINE

Formerly Çağdaş Tıp Dergisi

CONTENTS

YEAR 2023 VOLUME 13 ISSUE 3 e-ISSN 2667-7180

ORIGINAL ARTICLES

JOURNAL OF CONTEMPORARY MEDICINE

Formerly Çağdaş Tıp Dergisi

CONTENTS

YEAR 2023 VOLUME 13 ISSUE 3 e-ISSN 2667-7180

ORIGINAL ARTICLES

JOURNAL OF CONTEMPORARY MEDICINE

Formerly Çağdaş Tıp Dergisi

CONTENTS

YEAR 2023 VOLUME 13 ISSUE 3 e-ISSN 2667-7180

ORIGINAL ARTICLES

JOURNAL OF CONTEMPORARY MEDICINE

Formerly Çağdaş Tıp Dergisi

CONTENTS

YEAR 2023 VOLUME 13 ISSUE 3 e-ISSN 2667-7180

ORIGINAL ARTICLES

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Original Article / Orijinal Araştırma

The Relationship Between Type D Personality and Impulsivity in Medicine, Dentistry, and Nursing Students

Tıp, Diş Hekimliği ve Hemşirelik Öğrencilerinde D Tipi Kişilik ile Dürtüsellik Arasındaki İlişki

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Abstract

Aim: Type D personality is defined as a type in which negative affectivity (NA) and social inhibition (SI) are prominent. Type D personality is associated with psychiatric symptoms. The present study aims to investigate the relationship between Type D personality and impulsivity in a non-clinical population.

Material and Method: In total, 462 undergraduate health Professional students were recruited for the study. Subjects were evaluated using Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Barratt Impulsivity Scale-11 (BIS-11), and Type D Personality Scale (DS-14).

Results: The frequency of type D personality was 39.6%. The BAI, BDI, and BSI scores were higher in participants with Type D personality compared to the group without Type D personality. Correlation analysis demonstrated that Type D personality was positively correlated with the severity of depression and anxiety. Impulsivity scores measured by the BSI was posivitely correlated with Type D personality, depression, and anxiety scores. Regression analysis demonstrated that impulsivity was predicted by male sex and depression scores.

Conclusion: Type D personality was correlated with the severity of depression and anxiety. Depression scores and male sex predicted impulsivity.

Keywords: Type D personality, depression, anxiety, impulsivity

Öz

Amaç: D tipi kişilik negatif afektivite (NA) ve sosyal inhibisyonun (SI) belirgin olduğu bir kişilik tipi olarak tanımlanmaktadır. D tipi kişilik psikiyatrik semptomlarla ilişkilidir. Bu çalışmanın amacı klinik olmayan bir popülasyonda Tip D kişilik ile dürtüsellik arasındaki ilişkinin araştırılmasıdır.

Gereç ve Yöntem: Çalışmaya toplamda sağlık alanında eğitim gören 462 üniversite öğrencisi dahil edilmiştir. Katılımcılara Beck Anksiyete Ölçeği (BAI), Beck Depresyon Ölçeği (BDI), Barratt Dürtüsellik Ölçeği-11 (BIS-11) ve D Tipi Kişilik Ölçeği (DS-14) ile değerlendirilmiştir.

Bulgular: D tipi kişiliğin sıklığı % 39.6 idi. D tipi kişiliği olanlarda olmayanlarda göre BAI, BDI ve BIS ölçek skorları daha yüksek bulunmuştur. Korelasyon analizinde D tipi kişiliğin depresyon ve anksiyetenin şiddetiyle pozitif olarak korele olduğu gösterilmiştir. BIS ile ölçülen dürtüsellik skorlarının D tipi kişilik, depresyon ve anksiyete skorları ile pozitif yönde korele oldukları görülmüştür. Regresyon analizinde ise dürtüselliğin erkek cinsiyet ev depresyon skorları ile predikte edildiği gösterilmiştir.

Sonuç: D tipi kişiliğik depresyon ve anksiyete şiddetiyle koreledir. Depresyon puanları ve erkek cinsiyet dürtüselliği yordamaktadır.

Anahtar Kelimeler: Tip D kişilik, depresyon, anksiyete, dürtüsellik

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INTRODUCTION

In clinical practice, evaluation of personality is important in many ways. Type D or distressed personality is defined as a type in which negative affecttivity (NA) and social inhibition (SI) are prominent.[1,2] NA is the tendency to experience negative emotions such as anger, guilt, hostility, and depression across situations and time. NA is manifested in high levels of distress and dissatisfaction regardless of the time or situation. SI is the tendency to inhibit the expression of emotions and behaviors in social interactions to avoid disapproval.[3] Individuals with high levofs on both NA and SI are categorized as having Type D personalities.[4,5]

Type D personality has been widely studied, especially in the field of cardiology. Type D personality was found to be associated with increased mortality and morbidity burden, and poorer health-related quality of life in cardiovascular diseases.[6]

Recent studies have also demonstrated the relationship between Type D personality and psychiatric disorders. It has also been shown that type D personality is associated with symptoms of depression, anxiety, sleep problems, post-traumatic stress disorder, somatic symptoms, mental distress, suicidal ideas, passive coping, and less social support.[7-12]

Impulsivity is a key feature of many psychiatric disorders such as affective disorders, anxiety disorders, personality disorders, alcohol dependence, attention deficit hyperactivity disorder, and bulimia nervosa. Impulsivity is defined as a predisposition to have rapid and unplanned reactions to internal and external stimuli without regard to the negative consequences of these reactions to individuals and others.[13,14] It has been shown that both anxiety and depression are associated with increased impulsiveness.[15] Results of a population study demonstrated that there was an association between Type-D personality and suicidal ideation.[16] Moreover, in patients with major depression, Type D personality was associated with increased impulsivity and SI subscale scores were higher in depressed patients with a history of suicide attempts.[17,18]

So, these findings suggest that there may be a relation between Type-D personality and impulsivity.

Considering that one of the main concepts of Type D personality is social inhibition, increased impulsivity in these individuals is a condition to be investigated. To the best of our knowledge, there is no study investigating the relationship between Type D personality and impulsivity in a non-clinical population. For this purpose, this study aims to investigate the relation relationshipType D personality and impulsivity in a group of university students. As Type D personality is associated with depression and anxiety,[19,20] we also aimed to investigate this relationship by controllthe confounding factors such as depression and anxiety.

MATERIAL AND METHOD

Participants

All participants were from the health campus of our university. There are 1400 undergraduate students in the Faculty of Medicine, 891 students in the Faculty of Dentistry, and 880 students in the Faculty of Nursing. Sampling was calculated by using the quota sampling method. It was aimed to reach 423 people by assuming an alpha error level of 5%, a design effect of 1.5, and a sample power of 80%. Each faculty was accepted as a cluster and it was planned to recruit participants from each cluster according to the number of students. We reached 462 students, but 5 were excluded because of incomplete forms. A total of 457 students, of which 218 were from medical faculties, 114 from dental faculties, and, 125 from nursing departments, participated in the study.

Psychometric Scales

Sociodemographic Data Form: This form was developed by the authors for this research, and the age, sex, faculty, place of residency, level of income, family history of psychiatric disorders, previous psychiatric history, and substance use history of the participants were recorded on it.

Type-D Personality Scale-14 (DS-14): The DS-14 comprises the subscales of negative affectivity (NA) and social inhibition (SI) containing seven items each Individuals scoring greater than the cut-off value (≥10) for both subscales are classified as having a type-D personality.4 The Turkish version of DS-14 was shown to valid and reliable for clinical and research purposes.[21]

Beck Depression Inventory (BDI): This self-report questionnaire consists of 21 items and is indicative of the presence of significant depressive symptoms over a cut-off score of 17.[22] The adapted Turkish version of the inventory was used in this study which was shown to be valid and reliable by Hisli.[23]

Beck Anxiety Inventory (BAI): The BDI is composed of 21 self-assessment items that evaluate the severity of anxiety. depression. Each question inquires about the respondent's anxiety symptoms on a 4-point scale. A score of 22 or higher is indicative of moderate levels of anxiety.[24] The validity and reliability study was performed in Turkey by Ulusoy et al.[25]

Barratt İmpulsiveness Scale (BIS-11): BIS-11 is a 30-item self-report scale that assesses the appearance of impulsivity. There are 3 subscales that do not overlap with each other, such as non-planning, motor impulsiveness, and cognitive impulsiveness.[26] The scale was adapted to Turkish by Güleç et al.[27]

Procedure

After getting permission from the administration, all students were reached at the end of lecture hours at their faculties. After being informed about the study, the subjects filled out the sociodemographic data form,

Type D personality Scale-14 (DS-14), Beck Depression Inventory (BDI), Beck Anxiety Inventory (, BAI), and Barratt Impulsiveness Scale (BIS-11) in their lecture halls.

The study procedures were carried out in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 24. The variables were investigated using visual (histograms) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. In addition to the descriptive statistical methods (mean, standard deviation, and frequency), for the comparison of the quantitative data, the Chi-square test where appropriate, was used to compare the proportions in different groups. Spearman correlations were used to determine the strength of the relationship between the variables. For the multivariate analysis, the possible factors were identified in the logistic regression analysis to determine independent predictors of type D personality. A multiple linear regression model was used to identify independent predictors of impulsivity. The model fit was appropriate residual and goodness-of-fit statistics. A 5% type-1 error level was used to infer statistical significance.

RESULTS

Sample Characteristics

Of the 457 participants, 197 (42,7 %) were male and 265 (57,3) were female. As mentioned before, 218 of them were from medical faculties, 114 of them were from dental faculties, and 125 of them were from nursing departments. The mean age of all participants was 21.4±2.01 years.

82.6% (n=321) of the participants indicated that they had a past psychiatric history and 11.4% (n=52) stated that they had a family history of psychiatric disorder.

According to BDI and BAI, 18.3% of the participants had moderate to severe depression and 27.9% of the participants had moderate to severe anxiety respectively. As expected, both moderate to severe depression and anxiety were more prevalent in women compared to men (p=0.029 and p<0.001 respectively)

The prevalence of type-D personality in the present sample was 39.6%. The average total impulsivity score was 64±11; the average subscale scores were 17±4 for attention impulsivity, 21±5 for motor

impulsivity, and 25±5 for non-planning impulsivity. The distribution of sociodemographic and clinical variables of the participants with and without Type D personality are shown in **Table 1.**

Table 1. Comparison of demographic and clinical variables between groups.

		Group without type D personality		Group with type D personality		
		n	%	n	%	p
Age, years*		21.39±2.06		21.48±1.95		0.280
Sex	Male	115	59.3	79	40.7	0.786
	Female	158	60.5	103	39.5	
Faculty	Medicine (n=218)	117	53.9	100	46.1	0.001
	Dentistry (n=114)	65	57.0	49	43.0	
	Nursing (n=125)	91	73.4	33	26.6	
Class	1	57	58.2	41	41.8	0.009
	2	81	73.0	30	27.0	
	3	48	49.5	49	50.5	
	4	50	64.1	28	35.9	
	5	28	54.9	23	45.1	
	6	9	45.0	11	55.0	
Place of residence	Youth hostel	80	67.2	39	32.8	0.166
	House (alone)	35	55.6	28	44.4	
	House	157	57.9	114	42.1	
Past psychiatric history	Yes	234	62.1	143	37.9	0.030
	None	37	48.7	39	51.3	
Family history of psychiatric disorder	Yes	24	48.0	26	52.0	0.058
	None	247	61.9	152	38.1	
Alcohol and smoking	None	194	61.0	124	39.0	0.665
	Smoking	56	56.0	44	44.0	
	Alcohol	22	61.1	14	38.9	
Total BAI*		9.88±9.33		15.93±10.93		≤0.001
	Minimal-mild	223	68.0	105	32.0	
	Moderate-severe	50	39.7	76	60.3	
Total BDI*		8.68±7.74		15.81±10.05		≤0.001
	Minimal-mild	244	66.1	125	33.9	
	Moderate-severe	28	33.7	55	66.3	
Total BIS*		61.56±10.85		66.82±10.65		≤0.001

* Mean±standart deviation

Group Comparisons According to the Presence/Absence of Type D Personality

The group was divided into two groups according to the presence or absence of Type D personality. Comparisons between the group with type D personality and that without type D personality are given in **Table 1**. Faculty and class were different between groups (p=0.001 and p=0.009 respectively). The post-hoc analysis demonstrated that Type D personality was more prominent in the faculty of medicine and dentistry than nursing. It was seen that the difference in the class disappeared when the 2nd grades were removed from the group. The group without Type D personality had more past psychiatric history compared to the group with Type D personality (62.1 vs 37.9, p=0.030). The Total BAI, BDI, and BIS scores were significantly higher in the group with Type D personality compared to the group without Type D personality (p≤0.001 for all).

Correlation Analysis

Correlation analysis showed that there was a moderate positive correlation between BDI points with DS-14 scale points (p ≤0.001, r=.58) . There was also a weak positive correlation between BAI points with DS-14 scale points (p ≤0.001, r=.444) The BIS scores were positively but weakly correlated with BAI, BDI and DS-14 scale points (p ≤0.001 for all, r=.205, r=.318, r=.220). The results of the correlation analyses are shown in **Table 2**.

Table 2. The correlations between BAI, BDI, BSI and DS-14 scale scores of participants. (n=457)

		BAI	DS-14	BDI
DS-14	rho	0.444		
	p	≤0.001		
BDI	rho	0.497	0.548	
	p	≤0.001	≤0.001	
BIS	rho	0.205	0.220	0.318
	p	≤0.001	≤0.001	≤0.001

Regression Analysis

As there was a positive correlation between BIS scores with BDI, BAI, and DS-14 scale scores linear regression analysis was performed to determine independent predictors for impulsiveness. Linear regression analysis was performed taking the BSI score as the dependent variable and sex, age, BAI, BDI, and DS-14 scores as independent variables. The results showed that being male and the BDI scores were the predictors of BSI. In other words, the DS-14 was not a predictor of the BSI score. The results of the regression analyses are shown in **Table 3**.

Table 3: Linear regression analysis when BIS score was taken as dependent variable and sex, age, BAI, BDI and DS-14 scores as independent variables (n=457)

	Standardized coefficients (β)	t	OR	95% CI	p
Age. years	-0.005	-0.105	0.000	(-0.004-0.003)	0.916
Sex (ref. female)	0.135	2.773	0.021	(0.006-0.035)	0.006
BAI	0.096	1.654	0.019	(-0.004-0.042)	0.099
BDI	0.387	6.468	0.078	(0.055-0.102)	≤0.001
DS-14	-0.068	-1.182	-0.025	(-0.067-0.017)	0.238

CI: confidence interval

DISCUSSION

The objective of the present study was to investigate the relationship between Type D personality and impulsivity by controlling depression and anxiety in a group of health profession students. Participants with Type D personality had higher scores on BAI, BDI, and BSI scales. Correlation analysis demonstrated that Type D personality was positively correlated with the severity of depression (moderate) and anxiety (weak). Impulsivity scores measured by the BSI were positively but weakly correlated with Type D personality, depression, and anxiety scores. Regression analysis demonstrated that impulsivity was predicted by male sex and depression scores.

The participants of the present study were health profession students. Training in medicine and other health professions is associated with high levels of stress and psychological morbidity.[28] Our study showed that 18,3% of the participants had reported moderate to severe depression and 27,9% of the participants had reported moderate to severe anxiety. Health professions students report higher levels of depression and anxiety compared to their age-matched controls.[29,30] The symptoms of depression were reported to be between 8% and 70% in students of medical faculty in different studies.[31]

It was shown that other healthcare professional students were stressed similarly to medical students; even some groups could be in more mental distress compared to medical school students.[32,33] In line with this, but interestingly our study group reported a high level of past psychiatric history (82.6%) Since the question about psychiatric admission was not only limited to depression but involving all admission; this high percentage can be better understood. Of course, past psychiatric referral does not necessarily mean that the person has suffered from a mental disorder. Even so, this high level should be explored more. Both depression and anxiety were more prevalent in women compared to men in the present study. This gender difference was also reported in similar studies.[29,31]

The prevalence of type-D personality in the present sample was almost 40%. When it is taken into account that the prevalence of Type D personality is 21% in the general population 4; we can say that Type D personality is more common in health professional students compared to the general population. Studies investigating the prevalence of Type D personality in university students reveal different results from 31% to 43.3%.[20,34] The results were thought to vary according to the selected student groups

Participants with Type D personality reported more anxiety, and depression and they were more impulsive compared to participants without Type D personality. Type D personality was shown to be associated with depression, anxiety, and other psychiatric disorders.[7,9] Moreover, it was also shown that depressed individuals with Type D personalities were more impulsive and vulnerable to suicidality.[8] Type D personality was more prevalent in the faculty of medicine and dentistry compared to the faculty of the nursery. It is well known that personality traits are important in career choice. Relatively, it can be said that medicine and dentistry have more difficult entry conditions than nurseries in many faculties. Therefore, it can be argued that those who choose these difficult faculties have different personality traits than the normal population. Interestingly, past psychiatric history was more prevalent in the group without Type D personality. From this, it can be concluded that those with Type D personality traits are less likely to apply for psychiatry, even if they experience psychological distress.

The present study showed that Type D personality was positively correlated with the severity of depression (moderate) and anxiety (weak). Patients with type D personalities had an increased risk for both depression and anxiety.[19,35] In a study evaluating the effect of Type D personality in university students, it was demonstrated that Type D personality was associated with higher depressive symptoms. Type D personality was also correlated with depression and anxiety scores in addicted individuals.[36]

Impulsivity scores measured by the BSI were positively but weakly correlated with Type D personality, depression, and anxiety scores. Both depression and anxiety are associated with increased impulsiveness.[15] Positive correlations between depression, anxiety, and impulsivity is a well-known topics.[37] There is scarce knowledge about the relationship between type D personality and impulsivity. Similar to the present study, Park et al found a positive correlation between Type D personality scores and impulsivity scores measured by BIS-11 in depressed individuals.[17] There was no other study looking for an association between Type D personality and impulsivity in a non-clinical sample.

Regression analysis also demonstrated that impulsivity was predicted by male sex and depression scores. Men are generally thought to be more impulsive compared to women.[38] In the present study, while depression scores were associated with impulsivity, Type D personality and anxiety had no value for predicting impulsivity. Although Type D personality and impulsivity are correlated, the fact that Type D personality does not appear to have a role in predicting impulsivity can be interpreted as other factors that may play a role in this relationship. Park's study was conducted in a group with major depression and it was also shown that suicidal ideation was related to the NA subscale of Type D personality.[17,18] Therefore, studies in different clinical and non-clinical groups are needed to better understand the relationship between impulsivity and Type D personality.

To the best of our knowledge, this is the first study investigating the relationship between Type D personality and impulsivity in a non-clinical sample. The results of the present study must be interpreted in light of certain limitations. First of all, this study was conducted in a single center and in a subgroup of university students, which were generally shown to be more stressed compared to other university students. Additionally, the past psychiatric admission rate of our participants is very high. So, these make it difficult to generalize the study findings to the general population.

Although the lack of clinical interviews seems to be another limitation, the main purpose of the study is to investigate the findings in a non-clinical group. The cross-sectional design of the study can be mentioned as another limitation because we don't know if these participants will go on to experience these symptoms. But, it is the classical limitation of similar studies. It is not completely understood how class differences and the incidence of Type D personality change in student groups or what factors play a role in these findings. Probably, a small number of our study in a non-clinical sample and the fact that it was conducted in a special group of university students may have affected this result. Despite these limitations, the present study is valuable in terms of exploring the relationship between Type D personality and impulsivity while controlling for anxiety and depression.

CONCLUSION

We found that participants with Type D personality had more depressive, anxious, and impulsive compared to non-type D personality. there was a moderate positive correlation between BDI points with DS-14 scale points. Type D personality was positively correlated with the severity of depression and anxiety. Impulsivity was positively correlated with depression, anxiety, and Type D personality. Lastly, male sex and depression were predictors of impulsivity. Different studies including clinical and non-clinical samples in a follow-up design should provide better results to understand this topic.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Marmara University Clinical Research Ethical Committee (Date of approval: 12.04.2019, Approval Number: 09.2019.376)

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article / Orijinal Araştırma

The Role of the De Ritis Ratio in Acute Cholecystitis: A Retrospective Observational Study

De Ritis Oranının Akut Kolesistitteki Rolü: Retrospektif Gözlemsel Çalışma

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Abstract

Aim: Our primary aim was to evaluate the relationship between De-Ritis rate and short-term mortality in patients with cholecystitis. Our secondary aim was to evaluate the relationship between De-Ritis rate and short-term mortality in patients who underwent emergency surgery for acute cholecystitis.

Material and Method: This retrospective observational study was conducted on patients diagnosed with acute cholecystitis by laboratory parameters and ultrasound, and operated on who presented to the emergency medical clinic of University of Health Sciences, Ümraniye Education and Research Hospitalbetween June 1, 2020, and January 1, 2022. The relationship between De-Ritis rate and mortality was evaluated. The Statistical Package for Social Sciences (SPSS) software (v.20; Chicago, IL, USA) was used for all statistical analyses. All results with $p < 0.05$ were considered statistically significant.

Results: In our study, 174 patients were included, and 50.6% of our patients were women. The mean age was 59.0 (43.2 to 71.8). A total of 2.29% of our patients died. No statistically significant relationship was found between AST, ALT, CRP, albumin, and the De-Ritis ratio and mortality (p=0.584, p=0.533, p=0.517, p=0.07, p=0.399, respectively). When mortality rates in patients who underwent emergency surgery for acute cholecystitis were examined, no statistically significant correlation was found between AST, ALT, CRP, albumin, and De-Ritis rates and mortality (p=0.248, p=0.315, p=0.451, p=0.183, p=0.688, respectively)

Conclusion: De-Ritis rate was not found to be associated with mortality in patients with acute cholecystitis. De-Ritis rate was not associated with mortality in emergency operated patients who underwent emergency surgery for acute cholecystitis.

Keywords: Cholecystitis, AST, ALT, De-Ritis ratio

Öz

Amaç: Çalışmamızda primer amacımız kolesistit tanılı hastalarda De-Ritis oranı ile kısa dönem mortalite arasındaki ilişkiyi değerlendirmek idi. Sekonder amacımız ise akut kolesistit nedeni ile acil opere olan hastalarda De-Ritis oranının kısa dönem mortalite ile ilişkisini değerlendirmek idi.

Gereç ve Yöntem: Bu retrospektif gözlemsel çalışma, 1 Haziran 2020 ile 1 Ocak 2022 tarihleri arasında Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi acil servisine başvuran, labaratuvar parametreleri ve ultrason ile akut kolesistit tanısı alan hastalar ve ameliyat edilen hastalar üzerinde yapılmıştır. De-Ritis oranının mortalite ile ilişkisi değerlendirildi. Statistical Package for Social Sciences (SPSS) yazılımı (v.20; Chicago, IL, ABD) tüm istatistiksel analizler için kullanıldı. $p < 0.05$ olan tüm sonuçlar istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmamıza 174 hasta dahil edildi ve hastalarımızın %50,6'sı kadındı. Ortalama yaş 59.0 (43.2 ila 71.8) idi. Hastalarımızın toplam %2,29'u vefat etti. AST, ALT, CRP, albumin ve De-Ritis oranı ile mortalite arasında istatistiksel olarak anlamlı bir ilişki bulunmadı (sırası ile p=0,584, p=0,533, p=0,517, p=0,07, p=0,399). Akut kolesistit nedeni ile acil opere olan hastalarda mortalite oranları incelendiğinde AST, ALT, CRP, albumin ve De-Ritis oranları ile mortalite arasında istatistiksel olarak anlamlı bir ilişki bulunmadı (sırası ile p=0,248, p=0,315, p=0,451, p=0,183, p= 0.688)

Sonuç: De-Ritis oranı akut kolesistit tanılı hastalarda mortalite ile ilişkili bulunmadı. Aku kolesistit nedeni ile acil opere olan hastalarda da De-Ritis oranı mortalite ile ilişkili değildi.

Anahtar Kelimeler: Kolesistit, AST, ALT, De-Ritis oranı

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INTRODUCTION

Cholecystitis is an emergency surgical disease that may present with mild clinical symptoms or severe clinical findings, such as cholangitis and pancreatitis, characterized by gallbladder inflammation. An essential part of these is caused by gallstones.[1] The diagnosis is made by specific physical examination findings, laboratory tests, and radiological imaging techniques. The Tokyo criteria (TG18 Diagnostic Criteria and Severity Grading of Acute Cholecystitis) took their last updated form in 2018 and are still used in diagnosing cholecystitis.[2] C-reactive protein[3], neutrophil, lymphocyte[4] are well known systemic inflammatory biomarkers. Occurring after an inflammatory process, the effects of hematological parameters such as WBC (white blood cell), neutrophil, lymphocyte[5], C-reactive protein[6], hematological inflammatory indices[7], and CRP/albumin ratio[8] on the prognosis in patients with cholecystitis have been the subject of studies.

ALT (alanine aminotransferase), one of the clinical laboratory tests, is an aminotransferase from the enzyme group that reversibly catalyzes the conversion of alpha ketoacids to amino acids. It is active in the heart and skeletal muscle along with the liver, but specific ALT activity in the liver is more effective than in the heart and skeletal muscle. It is found in hepatocytes, and its height indicates a defect in the hepatocyte plasma membrane. AST (aspartate aminotransferase) is found mainly in the liver and skeletal muscle, brain, heart, lung, kidney, pancreas, leukocytes, and erythrocytes. It increases in skeletal muscle destruction and cardiac damage, particularly in liver diseases.[9,10]

The De-Ritis ratio (AST/ALT ratio) was first used by Fernando De Ritis in 1957[11], and the De-Ritis ratio began to be used in viral hepatitis, alcoholic hepatitis, and ischemic hepatitis.[12] The effect of the De-Ritis ratio, which is thought to be an indicator of liver damage, on the prognosis has been evaluated in various studies.[13-16] In patients with sepsis[13], patients with intestinal lung disease[14] and patients with COVID-19[15,16], patients diagnosed with cancer[17-25], and patients with clinical conditions and ischemic processes, for example, patients with cardiac arrest[26], patients with acute myocardial infarction[27] and patients with kidney damage during percutaneous coronary angiography[28], the effect of the De-Ritis ratio on prognosis was discussed. To the best of our knowledge, there have been no studies in the literature on the effect of the De-Ritis ratio on prognosis in patients with cholecystitis.

Aim

Our primary aim was to evaluate the relationship between De-Ritis rate and short-term mortality in patients with cholecystitis. Our secondary aim was to evaluate the relationship between De-Ritis rate and short-term mortality in patients who underwent emergency surgery for acute cholecystitis.

MATERIALS AND METHOD

Study Design

This retrospective cross-sectional observational study was conducted on patients diagnosed with AC who presented to the emergency medical clinic of University of Health Sciences, Ümraniye Education and Research Hospital between June 1, 2020, and January 1, 2022. Our hospital is a tertiary education and research institute with approximately 840 beds, receiving 2.9 million presentations per year. However, there are 600,000 applications per year to the emergency department.

Study population

This study included patients aged ≥18 years with clinically, radiologically, and laboratory-confirmed acute cholecystitis diagnoses and hemogram and biochemical parameters measured and registered by the Emergency Department. Patients aged <18 years, those with a history of trauma, incomplete data, patients whose mortality information could not be reached, and patients who died due to a reason other than cholecystitis or cholecystitis complication who refused to participate in the study were excluded.

Data Collection

The data of patients admitted to the emergency department and diagnosed with cholecystitis were collected retrospectively. These data included demographic characteristics, age, sex, comorbid diseases, laboratory findings (neutrophils, lymphocytes, eosinophils, basophils, platelets, WBCs (white blood cells), hemoglobin, hematocrit, mean platelet volume, mean corpuscular volume, C-reactive protein, total, direct, indirect bilirubin, BUN (blood urea nitrogen), creatinine, AST, ALT, De Ritis ratio (AST/ALT), length of hospital stay (LOS) and mortality. The radiological technique we used in the diagnosis was ultrasound. Emergency operated and non-operated patients were also examined. The patients were divided into two groups—nonsurvivors and survivors—based on their status in Turkey's National Death Notification System. The nonsurvivor group consisted of cholecystitis-related deaths, and 30-day mortality was recorded. Intensive care unit admission rates and length of hospital stay were recorded using the hospital's data system.

The Tokyo Guidelines 2013 (TG13) and The Tokyo Guidelines 2018 (TG 18) severity grading for acute cholecystitis

"Grade III (severe)" acute cholecystitis is associated with dwysfunction of any one of the following organs/systems:

1. Cardiovascular dysfunction: hypotension requiring treatment with dopamine ≥5 µg/kg per min, or any dose of norepinephrine.
2. Respiratory dysfunction: PaO_2/FiO_2 ratio <300.
3. Neurological dysfunction: decreased level of consciousness.
4. Renal dysfunction: oliguria, creatinine >2.0 mg/dl.
5. Hematological dysfunction: platelet count <100,000/mm³.

6. Hepatic dysfunction: PT-INR >1.5.

"Grade II (moderate)" acute cholecystitis is associated with any one of the following conditions:

1. Palpable tender mass in the right upper abdominal quadrant.
2. Elevated WBC count (>18,000/mm³).
3. Duration of complaints >72 hours.
4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis).

"Grade I (mild)" acute cholecystitis does not meet the criteria of "Grade III" or "Grade II" acute cholecystitis. It can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) software (v.20; Chicago, IL, USA) was used for all statistical analyses. All results with $p < 0.05$ were considered statistically significant. The normality of continuous data was assessed using the Shapiro–Wilk test. Categorical variables are presented as numbers (percentages), continuous variables are presented as medians (ranges), and quantitative variables are presented as medians (interquartile ranges; 25th-75th percentiles). Categorical data were compared using Chi-square tests and Fisher's exact tests. Continuous data were compared pairwise using Mann–Whitney tests.

Ethics

The study was conducted with the permission of the University of Health Sciences, Ümraniye Education and Research Hospital Ethics Committee (Date: 20/10/2022, Decision No: B.10.1.TKH.4.34.H.GP.0.01/322). The ethical rules and the principles of the Declaration of Helsinki performed out all procedures.

RESULTS

In our study, 174 patients were included, and 50.6% of our patients were women. The mean age was 59.0 (43.2 to 71.8). A total of 2.29% of our patients died. Coronary artery disease and chronic renal failure, which are comorbid diseases, had a statistically significant relationship with mortality (p=0.006, p=0.007, respectively). It was determined that there was a statistically significant relationship between low hemoglobin and hematocrit and mortality. (p=0.006, p=0.003, respectively). No statistically significant relationship was found between AST, ALT, CRP, albumin, and the De-Ritis ratio and mortality (p=0.584, p=0.533, p=0.517, p=0.07, p=0.399, respectively). The demographic characteristics and laboratory findings of the patients are given in **Table 1**.

A total of 39.66% of our patients underwent surgery. Only one patient died from the operation (1.4%). No statistically significant correlation was found between comorbid diseases and the patients being operated on (**Table 2**). There was no statistically significant relationship between AST, ALT, CRP, albumin, and the De-Ritis ratio and mortality between operated and non-operated patients (p=0.069, p=0.095, p=0.353, p=0.535, p=0.89, respectively). (**Table 2**)

When mortality rates in operated patients were examined, no statistically significant correlation was found between AST, ALT, CRP, albumin, and De-Ritis rates and mortality (p=0.248, p=0.315, p=0.451, p=0.183, p=0.688, respectively) (**Table 3**). No statistically significant correlation was found between AST, ALT, CRP, albumin and De-Ritis rates and mortality in patients who underwent surgery and had a hospital stay longer than seven days (p=0.668, p=0.610, p=0.835, p=0.303, p=0.871, respectively).

DISCUSSION

Our study found that the De-Ritis ratio in patients diagnosed with cholecystitis was statistically insignificant in predicting mortality. AST, ALT, albumin, and CRP levels were also ineffective in predicting mortality in all patients. Additionally, the De-Ritis ratio was not associated with surgical operations in patients with cholecystitis. There was no difference in the De Ritis ratio in patients who underwent surgery compared to patients who did not undergo surgery. Our study showed that the De-Ritis ratio has no prognostic significance in cholecystitis patients. According to the Tokyo guidelines classification, in our study, it was observed that grade III did not have superiority over other grades in terms of mortality. To the best of our knowledge, no study has examined the relationship between cholecystitis and the De-Ritis ratio.

In addition, the relationship between the De-Ritis ratio and patient prognosis in sepsis[13], lung diseases[14,16], and cancers[17] was examined. The effect of the De-Ritis ratio on the prognosis in patients with sepsis progressing with an inflammatory process was investigated, and Schupp et al. found that the De-Ritis ratio and bilirubin values on the 1st, the third, fifth, and seventh days were associated with mortality in patients with septic shock. On the 30th day, although it could determine mortality, the De-Ritis ratio was observed to be superior in determining mortality compared to bilirubin values.[13] In a retrospective study, the De-Ritis ratio was found to be a predictive factor for mortality in patients with intestinal lung disease-related polymyositis-dermatomyositis.[14] In a study conducted on patients diagnosed with COVID-19, the De-Ritis ratio was found to be statistically significantly higher in patients diagnosed with COVID-19 than in healthy people.[15] In a study conducted on patients diagnosed with COVID-19 with respiratory disease, similar to our study, no statistically significant relationship was found between having a history of liver disease or elevated AST and ALT and mortality. However, it was found that there was a statistically significant relationship between a high De-

Table.1 Relationship of demograhic parameters, laboratory parameters, De-Ritis ratio with mortality

	Survivor n=170 (97.71 %)	Nonsurvivor n=4 (2.29%)	Total (n=174)	p value
Age median (IQR)	58.5 (43.0 to 71.0)	81.0 (75.5 to 83.0)	59.0 (43.2 to 71.8)	0.030
Gender n(%)				0.323
Female	85.0 (50.0%)	3.0 (75.0%)	88.0 (50.6%)	
Male	85.0 (50.0%)	1.0 (25.0%)	86.0 (49.4%)	
Comorbidities n(%)				
Hipertension	76.0 (44.7%)	3.0 (75.0%)	79.0 (45.4%)	0.229
Diabetes Mellitus	35.0 (20.6%)	1.0 (25.0%)	36.0 (20.7%)	0.830
Malignancy	3.0 (1.8%)	0.0 (0.0%)	3.0 (1.7%)	0.789
Alzheimer	3.0 (1.8%)	0.0 (0.0%)	3.0 (1.7%)	0.789
Chronic Obstructive Pulmonary Disease	10.0 (5.9%)	1.0 (25.0%)	11.0 (6.3%)	0.120
Coronary artery disease	32.0 (18.8%)	3.0 (75.0%)	35.0 (20.1%)	0.006
Asthma	15.0 (8.8%)	0.0 (0.0%)	15.0 (8.6%)	0.534
Heart Failure	9.0 (5.3%)	0.0 (0.0%)	9.0 (5.2%)	0.637
Chronic Renal Failure	4.0 (2.4%)	1.0 (25.0%)	5.0 (2.9%)	0.007
Cerebrovascular Disease	10.0 (5.9%)	0.0 (0.0%)	10.0 (5.7%)	0.617
Laboratuary parameters Median (IQR)				
WBC (103µ/L)	12.9(10.5- 16.2)	9.7 (8.6 -11.9)	12.9 (10.3-16.2)	0.182
Neutrophil (103µ/L)	10.5 (8.2-13.6)	7.9 (6.6-10.0)	10.5 (8.0-13.6)	0.265
Monocyte (103µ/L)	0.7 (0.5-0.9)	0.7 (0.6-0.8)	0.7 (0.5-0.9)	0.928
Lymphocyte (103µ/L)	1.6 (1.0-2.2)	1.1 (0.9-1.5)	1.6 (1.0-2.2)	0.396
Eosinophil	0.1 (0.0-0.1)	0.0 (0.0-0.1)	0.1 (0.0-0.1)	0.758
Basophil	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.951
RBC	4.6 (4.3-5.0)	3.2 (3.0-3.5)	4.6 (4.3-5.0)	0.003
Hemoglobin (g/dl)	13.2 (12.3-14.4)	9.7 (9.0-10.9)	13.2 (12.3-14.4)	0.006
Hematokrit (%)	40.3 (37.7-43.6)	30.8 (29.3-33)	40.0 (37.5-43.3)	0.003
MCV (fl)	86.7 (83.9-90.1)	96.8 (86.8-105)	86.7 (83.9-90.3)	0.169
RDW (fl)	13.6 (13.0-14.4)	14.4 (13.8-15.1)	13.6 (13.1-14.4)	0.175
Platelet (103µ/L)	247.5 (207.5- 313)	210.5(181.8-277.5)	247.0(207-313.0)	0.460
MPV (fl)	9.4 (8.6-10.3)	9.6 (9.2-10.1)	9.5 (8.6-10.3)	0.767
PDW (%)ALT (IU/L)	16.2 (15.9-16.5)31.0 (17.0- 112.8)	16.3 (16.1-16.6)66.0 (27.0-115.8)	16.2 (15.9-16.5)31.5 (17-112.8)	0.6330.833
Albumin (g/dl)	38.5 (35.0- 42.0)	34.5 (28.6-37.2)	38.1 (35.0-42.0)	0.070
AST (IU/L)	34.0 (22.0-104.2)	97.5 (72.0-123.8)	34.0 (22-105.8)	0.584
CRP (mg/ml)	63.5 (11.0-150.2)	129 (94.2-138.2)	64.0 (11.0-148)	0.517
BUN (mg/dL)	32.1 (23.5-40.7)	46.0 (42.3- 48.2)	32.1 (23.5-40.7)	0.085
Creatinine (mg/dL)	0.8 (0.7-1.0)	1.1 (0.8-1.4)	0.8 (0.7-1.1)	0.313
Total Bilirubin (mg/dL)	1.2 (0.7-2.0)	0.9 (0.8-1.4)	1.2 (0.7-2.0)	0.633
Direkt Bilirubin (mg/dL)	0.4 (0.3-0.9)	0.4 (0.3-0.9)	0.4 (0.3-0.9)	0.833
Indirekt Bilirubin(mg/dL)	0.7 (0.4-1.1)	0.5 (0.4-0.6)	0.7 (0.4-1.1)	0.289
De-Ritis Ratio	1.2 (0.8-1.6)	1.3 (1.1-1.8)	1.2 (0.8-1.6)	0.399
LHOS Median (IQR)	4.0 (3.0-6.0)	2.0 (2.0-3.2)	4.0 (3.0-6.0)	0.118
surgery	68.0 (40.0%)	1.0 (25.0%)	69.0 (39.7%)	0.544
Tokyo 2018 severity grade				0.987
Grade 1	84.0 (49.4%)	2.0 (50.0%)	86.0 (49.4%)	
GradeII	38.0 (22.4%)	1.0 (25.0%)	39.0 (22.4%)	
Grade III	48.0 (28.2%)	1.0 (25.0%)	49.0 (28.2%)	

(WBC, white blood cell; RBC, red blood cells; MCV, mean corpusculer volüme; RDW, red cell distribution width; MPV: mean platelet volüme; PDW, Platelet Distribution Width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; BUN, blood urea nitrogen; LHOS, length of hospital stay/day)

Table.2 Relationship of demograhic parameters, laboratory parameters, De-Ritis ratio with operation status

	Non-operated n=105(60.34%)	Operated (n=69)(39.66%)	Total(n=174)	p value
Age median(IQR)	59.0 (43.0to74.0)	59.0 (44.0to71.0)	59.0 (43.2to71.8)	0.884
Gender n(%)				0.068
Female	59.0 (56.2%)	29.0 (42.0%)	88.0 (50.6%)	
Male	46.0 (43.8%)	40.0 (58.0%)	86.0 (49.4%)	
Comorbidities n(%)				
Hipertension	49.0 (46.7%)	30.0 (43.5%)	79.0 (45.4%)	0.679
Diabetes Mellitus	17.0 (16.2%)	19.0 (27.5%)	36.0 (20.7%)	0.071
Malignancy	2.0 (1.9%)	1.0 (1.4%)	3.0 (1.7%)	0.821
Alzheimer	2.0 (1.9%)	1.0 (1.4%)	3.0 (1.7%)	0.821
Chronic Obstructive Pulmonary Disease	5.0 (4.8%)	6.0 (8.7%)	11.0 (6.3%)	0.297
Coronary artery disease	23.0 (21.9%)	12.0 (17.4%)	35.0 (20.1%)	0.468
Asthma	6.0 (5.7%)	9.0 (13.0%)	15.0 (8.6%)	0.09
Heart Failure	7.0 (6.7%)	2.0 (2.9%)	9.0 (5.2%)	0.272
Chronic Renal Failure	2.0 (1.9%)	3.0 (4.3%)	5.0 (2.9%)	0.345
Cerebrovascular Disease	6.0 (5.7%)	4.0 (5.8%)	10.0 (5.7%)	0.982
Laboratuary parameters Median (IQR)				
WBC (103µ/L)	12.6 (10.3-16.1)	13.0 (10.6-16.2)	12.9 (10.3-16.2)	0.763
Neutrophil (103µ/L)	10.4 (8.2-13.8)	10.5 (7.9-13.4)	10.5 (8.0-13.6)	0.797
Monocyte (103µ/L)	0.7 (0.5-0.9)	0.7 (0.4-0.9)	0.7 (0.5-0.9)	0.510
Lymphocyte (103µ/L)	1.5 (1.0-2.2)	1.7 (1.0-2.2)	1.6 (1.0-2.2)	0.404
Eosinophil	0.1 (0.0-0.1)	0.0 (0.0-0.1)	0.1 (0.0-0.1)	0.456
Basophil	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.072
RBC	4.6 (4.2-5.1)	4.6 (4.3-4.9)	4.6 (4.3-5.0)	0.296
Hemoglobin (g/dl)	13.4 (12.4-14.5)	13.0 (12.0-14.1)	13.2 (12.3-14.4)	0.184
Hematokrit (%)	40.3 (37.8-43.8)	39.1 (36.9-42.8)	40.0 (37.5-43.3)	0.288
MCV (fl)	86.6 (84.0-90.0)	86.7 (83.6-90.9)	86.7 (83.9-90.3)	0.862
RDW (fl)	13.8 (13.2-14.5)	13.5 (12.9-14.2)	13.6 (13.1-14.4)	0.122
Platelet (103µ/L)	241.0 (196.0-302)	257.0 (225.0-339)	247.0 (207.0-313)	0.042
MPV (fl)	9.5 (8.8-10.3)	9.3 (8.5-10.4)	9.5 (8.6-10.3)	0.969
PDW (%)	16.3 (16.0-16.6)	16.1 (15.8-16.4)	16.2 (15.9-16.5)	0.018
ALT (IU/L)	36.0 (18.0-127.0)	27.0 (16.0-62.0)	31.5 (17.0-112.8)	0.095
Albumin (g/dl)	38.0 (34.0-42.0)	38.6 (35.0-43.0)	38.1 (35.0-42.0)	0.535
AST (IU/L)	42.0 (23.0-162.0)	31.0 (22.0-49.0)	34.0 (22.0-105.8)	0.069
CRP (mg/ml)	61.0 (10.0-143.0)	74.0 (16.0-157.0)	64.0 (11.0-148.0)	0.353
BUN (mg/dL)	34.2 (23.5-42.8)	32.1 (23.5-38.5)	32.1 (23.5-40.7)	0.808
Creatinine (mg/dL)	0.9 (0.7-1.1)	0.8 (0.7-1.0)	0.8 (0.7-1.1)	0.126
Total Bilirubin (mg/dL)	1.3 (0.8-2.2)	1.0 (0.6-1.7)	1.2 (0.7-2.0)	0.051
Direkt Bilirubin (mg/dL)	0.5 (0.3-1.2)	0.4 (0.2-0.7)	0.4 (0.3-0.9)	0.049
Indirekt Bilirubin (mg/dl)	0.7 (0.5to1.1)	0.6 (0.4to0.9)	0.7 (0.4-1.1)	0.143
De-Ritis Ratio	1.2 (0.8to1.6)	1.2 (0.8to1.8)	1.2 (0.8-1.6)	0.890
LHOS Median (IQR)	4.0 (3.0to7.0)	4.0 (3.0to6.0)	4.0 (3.0-6.0)	0.369
Mortality	3.0 (2.9%)	1.0 (1.4%)	4.0 (2.3%)	0.544

(WBC, white blood cell; RBC, red blood cells; MCV, mean corpusculer volüme; RDW, red cell distribution width; MPV: mean platelet volüme; PDW, Platelet Distribution Width; ALT, alanine aminotransferase; AST, aspartate aminotransferase, CRP, C-reactive protein; BUN, blood urea nitrogen; LHOS, length of hospital stay/day)

Table. 3 Relationship between laboratory parameters and De-Ritis rate and mortality in operated patients

	Survivor n=68	Non-survivor n=1	Total (n=69)	p value
Age	59.0 (43.8-71.0)	59.0 (59.0-59.0)	59.0 (44.0-71.0)	0.980
Laboratuary parameters Median (IQR)				
WBC (103µ/L)	12.9 (10.6-15.7)	16.8 (16.8-16.8)	13.0 (10.6-16.2)	0.340
Neutrophil (103µ/L)	10.5 (7.9-13.3)	14.8 (14.8-14.8)	10.5 (7.9-13.4)	0.292
Monocyte (103µ/L)	0.7 (0.4-0.9)	0.8 (0.8-0.8)	0.7 (0.4-0.9)	0.725
Lymphocyte (103µ/L)	1.7 (1.0-2.2)	1.2 (1.2-1.2)	1.7 (1.0-2.2)	0.514
Eosinophil	0.0 (0.0-0.1)	0.0 (0.0-0.0)	0.0 (0.0-0.1)	0.762
Basophil	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.778
RBC	4.6 (4.3-4.9)	3.1 (3.1-3.1)	4.6 (4.3-4.9)	0.088
Hemoglobin (g/dl)	13.0 (12.0-14.1)	8.9 (8.9-8.9)	13.0 (12.0-14.1)	0.097
Hematokrit (%)	39.4 (36.9-42.8)	28.1 (28.1-28.1)	39.1 (36.9-42.8)	0.097
MCV (fl)	86.7 (83.6-90.9)	90.7 (90.7-90.7)	86.7 (83.6-90.9)	0.422
RDW (fl)	13.5 (12.9-14.2)	13.6 (13.6-13.6)	13.5 (12.9-14.2)	0.841
Platelet (103µ/L)	256 (223.8-336.0)	438 (438-438)	257.0 (225-339)	0.132
MPV (fl)	9.4 (8.5-10.4)	8.1 (8.1-8.1)	9.3 (8.5-10.4)	0.191
Pct	0.2 (0.2-0.3)	0.3 (0.3-0.3)	0.2 (0.2-0.3)	0.238
PDW (%)	16.1 (15.8-16.4)	15.9 (15.9-15.9)	16.1 (15.8-16.4)	0.513
ALT(IU/L)	26.5 (16.0-56.8)	98.0 (98.0-98.0)	27.0 (16.0-62.0)	0.315
Albumin (g/dl)	39.0 (35.6-43.0)	32.0 (32.0-32.0)	38.6 (35.0-43.0)	0.183
AST(IU/L)	30.5 (21.5-48.2)	102.0 (102.0-102.0)	31.0 (22.0-49.0)	0.248
CRP (mg/ml)	71.5 (15.0-158.2)	135.0 (135.0-135.0)	74.0 (16.0-157.0)	0.451
BUN (mg/dL)	31.0 (23.5-39.1)	34.2 (34.2-34.2)	32.1 (23.5-38.5)	0.782
Creatinine (mg/dL)	0.8 (0.7-1.0)	0.7 (0.7-0.7)	0.8 (0.7-1.0)	0.422
Total Bilirubin (mg/dL)	1.0 (0.6-1.7)	1.0 (1.0-1.0)	1.0 (0.6-1.7)	0.880
Direkt Bilirubin (mg/dL)	0.4 (0.2-0.7)	0.5 (0.5-0.5)	0.4 (0.2-0.7)	0.514
Indirekt Bilirubin	0.6 (0.4-0.9)	0.4 (0.4-0.4)	0.6 (0.4-0.9)	0.547
De-Ritis Ratio	1.2 (0.8-1.8)	1.0 (1.0-1.0)	1.2 (0.8-1.8)	0.688
LHOS Median (IQR)	4.0 (3.0-6.0)	2.0 (2.0-2.0)	4.0 (3.0-6.0)	0.139

(WBC, white blood cell; RBC, red blood cells; MCV, mean corpusculer volüme; RDW, red cell distribution width; MPV: mean platelet volüme; PDW, Platelet Distribution Width; ALT, alanine aminotransferase; AST, aspartate aminotransferase, CRP, C-reactive protein; BUN, blood urea nitrogen; LHOS, length of hospital stay/day)

Ritis ratio and mortality.[16]

It's shown that the rate of De-Ritis was more frequently investigated in patients with cancer in the literature. The rate of De-Ritis, which can be obtained quickly and easily, has also been investigated in patients with many different malignancies.[17-19] In a study examining the relationship between colorectal and lung cancers and mortality, the De-Ritis ratio was found to have a significant relationship with both cancer incidence and mortality in cancer patients.[17] In a meta-analysis, the De-Ritis ratio was found to be effective in determining the prognosis of liver cancers, renal cell cancers, and gallbladder cancers.[18] In a retrospective study conducted on patients with hepatocellular cancer and including 1147 patients, it was observed that the preoperative De-Ritis ratio could predict the postoperative prognosis in patients with hepatitis B and hepatitis C-related cancer.[19] In a study conducted by Ghahari et al. on 89 patients with urethral bladder cancer who underwent radical cystectomy, they found that the average De-Ritis ratio was effective in the survey, and a high De-Ritis ratio was associated with mortality.[20] In another study, a similarly low De-Ritis ratio was found to be significant in disease-specific survival and overall survival.[21] The effect of the De-Ritis ratio on the prognosis before the operation was evaluated in patients who underwent surgery for prostate cancer, and it was determined that, contrary to our study, the De-Ritis ratio could be used as a risk factor.[22] Jadhav et al., on the other hand, found that the De-Ritis ratio could predict prognosis in patients diagnosed with prostate cancer.[23] In patients with testicular tumors who underwent orchiectomy, it was found that the rate of De-Ritis was not statistically significantly higher than in patients who underwent varicocelectomy.[24] Our study found that the De-Ritis ratio in operated patients was statistically insignificant in determining the prognosis.

In addition to studies on malignancy, clinical conditions with ischemic origin were also included in the studies. In a study conducted on patients brought to the hospital with cardiac arrest, 57% of the patients died during hospital follow-up. The high De-Ritis ratio was statistically significantly correlated with hospital mortality and intensive care mortality.[26] A study including 3000 patients diagnosed with acute myocardial infarction found a statistically significant correlation between a high De-Ritis ratio in cardiac mortality and three-year mortality. However, in the same study, it was also found that the De-Ritis ratio was moderately sensitive in terms of determining mortality in the postangio period and was not

superior to other risk prediction models in terms of mortality.[27] In a study conducted on patients who developed acute kidney injury associated with elective percutaneous coronary intervention, AST and ALT values were found to be higher than those in patients who did not develop acute kidney injury after angiography. The de-Ritis ratio was statistically significantly higher in patients with acute kidney injury.[28]

The De-Ritis ratio, which is discussed as to whether it is an indicator of liver injury or not, was also investigated in patients with thoracoabdominal trauma, regardless of liver injury. In a study conducted by Su et al. with 2248 thoracoabdominal trauma patients, mortality was found to be statistically significantly higher in the group with a De-Ritis ratio higher than >1.64; there was no statistically significant difference in mortality between those with a De-Ritis ratio <1.20 and those with a De-Ritis ratio between 1.20-1.64.[29] In a study investigating the rate of De-Ritis in 351 patients with extensive burns, a statistically significant relationship was found between AST, ALT, De-Ritis ratios, and mortality, and it was found that the De-Ritis ratio was superior to albumin in determining prognosis.[30] In a study conducted on patients with upper gastrointestinal bleeding treated in the intensive care unit, there was a statistically significant relationship between low albumin and mortality, and similar to our study, the De-Ritis ratio was not found to be statistically significant with mortality.[31]

Limitations

There are many limitations in our study. Data from our patients were collected retrospectively. Cholecystitis with and without gallstones was not differentiated, and all acute cholecystitis cases were included in the study. Therefore, classification according to etiology was not made. The study did not include those who applied to the emergency department with a clinical condition other than cholecystitis. Therefore, the number of patients was limited. Since death due to cholecystitis is rare, our mortality rate was also low. The first admission laboratory examinations of the patients were included in the study. Follow-up laboratory values during hospitalization were not taken.

CONCLUSION

De-Ritis rate was not found to be associated with mortality in patients with acute cholecystitis. De-Ritis rate was not associated with mortality in emergency operated patients who underwent emergency surgery for acute cholecystitis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of the University of Health Sciences, Ümraniye Education and Research Hospital Ethics Committee (Date: 20/10/2022, Decision No: B.10.1.TKH.4.34.H.GP.0.01/322).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Bibliographic Analysis of Articles on Laparoscopic Hysterectomy in The Field of Obstetrics and Gynecology

Kadın Hastalıkları ve Doğum Araştırma Alanında Laparoskopik Histerektomi ile İlgili Makalelerinin Bibliografik Analizi

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Private Practice

Abstract

Aim: This bibliometric study aimed to analyze published articles in the field of laparoscopic hysterectomy in order to identify their characteristics and trends.

Material and Method: The analysis covered all studies that had been published on laparoscopic hysterectomy that were published between 1992 and December 31, 2021. Bibliometric data was gathered from the Web of Science database, and VOSviewer software was used to construct bibliometric diagrams.

Results: A total of 993 articles according to the search criteria. 12.79% of the articles were published as open access and 96.375% of them were in English. Since 2010, 57% of articles have been published.These articles had an h-index of 70, a total of 23538 citations, and an average of 23.7 citations per article. Although the number of publications about laparoscopic hysterectomy changes from year to year, it peaked in 2015 (number of publications was 59) and it had the highest citation numbers (n=1800) in 2021. 3448 authors contributed to the publication of scholarly works on LH. Prof. Fabio Ghezzi from the University of Insubria (Italy) was the most published author on LH with 25 articles. Prof. Fabio Ghezzi's articles on LH were cited 735 times (29.4 per article). The majority of the articles were published by affiliates in Italy and the United States.

Conclusions: This study represents the first bibliometric analysis of laparoscopic hysterectomy. Laparoscopic hysterectomy research has declined after 2021. This situation; It may have resulted from the extraordinary burden placed on the healthcare system by the COVID-19 pandemic. Developing nations should think about increasing research funding to produce substantial research that can serve as the foundation for locally applicable, evidence-based laparoscopic hysterectomy interventions.

Keywords: Bibliometrics, citation analysis, laparoscopic hysterectomy, obstetrics

Öz

Amaç: Bu bibliyometrik çalışma, laparoskopik histerektomi alanında yayınlanmış makalelerin özelliklerini ve eğilimlerini belirlemek amacıyla analiz etmeyi amaçlamaktadır.

Gereç ve Yöntem: Analiz, 1992 ile 31 Aralık 2021 arasında yayınlanan laparoskopik histerektomi (LH) ile ilgili yayınlanmış tüm çalışmaları kapsıyordu. Bibliyometrik veriler Web of Science veri tabanından toplandı ve bibliyometrik diyagramlar oluşturmak için VOSviewer yazılımı kullanıldı.

Bulgular: Arama kriterlerine göre toplam 993 makale sağlandı. Makalelerin %12,79'u açık erişim olarak yayınlandı ve %96,375'i İngilizce idi. Makalelerin %57'si 2010 yılından bu yana yayınlanmıştır. Bu makalelerin h-index'i 70, toplam 23538 atıf ve makale başına ortalama 23,7 atıf vardı. LH ile ilgili yayın sayısı yıldan yıla değişmekle birlikte 2015 yılında zirve yapmış (yayın sayısı 59) ve en yüksek atıf sayısına (n=1800) 2021 yılında sahip olmuştur. 3448 yazar bilimsel çalışmaların yayınlanmasına katkıda bulunmuştur. LH'de. Insubria Üniversitesi'nden (İtalya) Prof. Fabio Ghezzi, 25 makale ile LH konusunda en çok yayın yapan yazar olmuştur. Prof. Fabio Ghezzi'nin LH ile ilgili makalelerine 735 kez (makale başına 29,4) atıf yapıldı. Makalelerin çoğu İtalya ve Amerika Birleşik Devletleri'ndeki bağlı kuruluşlar tarafından yayınlandı.

Sonuç: Bu çalışma, laparoskopik histerektominin ilk bibliyometrik analizini temsil etmektedir. Laparoskopik histerektomi araştırmaları 2021 yılından sonra azalmıştır. Bu durum COVID-19 pandemisinin sağlık sistemine bindirdiği olağanüstü yükten kaynaklanmış olabilir. Gelişmekte olan ülkeler, yerel olarak uygulanabilir, kanıta dayalı laparoskopik histerektomi müdahaleleri için temel oluşturabilecek önemli araştırmalar üretmek için araştırma fonlarını artırmayı düşünmelidir.

Anahtar Kelimeler: Bibliyometrik, atıf analizi, laparoskopik histerektomi, doğum

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INTRODUCTION

After Caesarean sections, hysterectomy is the most common gynecological procedure, and laparoscopic access to uterus removal is one of the modern techniques demonstrating a moderate but constant rise over time.[1] Recently, laparoscopic hysterectomy (LH) techniques have grown. This technique was initially used as a diagnostic tool for infertile women. Later, as technology advanced, it was utilized to do surgery on a tiny area of the ovaries and fallopian tubes. Today, it is believed that every gynecological procedure can be carried out laparoscopically.[2]

The following factors are debatable when it comes to LH indications and contraindications: malignant gynecological tumors, uterine size, and high body mass index. When endometrial, cervical, and ovarian cancer are in the early stages the LH technique may be an option.[1] As long as adequate expertise has been gathered and the technical specifics at different phases of the operation are properly adhered to, the LH technique is safe and practical for general gynecological surgical treatment.[3]

Annual worldwide hysterectomies done laparoscopically have significantly grown since the first publication on LH in 1989.[4] LH now accounts for up to 15% of all hysterectomies carried out in the United States of America (USA), indicating that the use of laparoscopy for all or a portion of hysterectomy has gained widespread acceptance. Laparoscopic hysterectomy is clearly associated with a shorter hospital stay and a quicker recovery time than laparotomy, according to a recent Cochrane analysis. Regarding the frequency of pelvic support disorders or sexual function, there is no research to suggest that a supracervical hysterectomy is preferable to a total hysterectomy.[5]

A bibliometric analysis can help identify influential articles that have influenced medical practice and spawned new research ideas.[6-13]

In the topic of obstetrics and gynecology, several bibliometric studies have been examined.[14-19] On the other hand, LH has not been the subject of a comparable bibliometric study. Thus, we desired to evaluate the evolution of the number of publications and citations over time, to identify the most prolific countries, researchers, and journals, and to lead future scientific research.

MATERIAL AND METHOD

Bibliometric Methodology

We identified the LH publications using the Web of Science Core Collection. The Web of Science Core Collection includes the Science Citation Index Expanded (SCIE) as well as other citation indexes and covers articles published from 1970 to 2022.[20] We used 1992 to December 2021 as the timespan and SCIE as the Wos index. We only retrieved the articles from the obstetric and gynecology research area.

In the title, the keyword "laparoscopic hysterectomy" was utilized as a term for database searching. The Vosviewer (Version 1.6.14) program was additionally employed to display data bibliometric linkages and mapping. The quantity of publications, the typical number of citations per article, and the H-index were examined and visualized using Microsoft Excel 2016. In the meantime, the images and tables were made using Microsoft Excel 2016.

Documents published in 2022 were not included in the study as the year was still running.

Summary of the search criteria: Results for laparoscopic hysterectomy (Title) and 2022 (Exclude – Publication Years) and 1991 or 1990 or 1989 or 1982 (Exclude – Publication Years) and Science Citation Index Expanded (SCI-EXPANDED) (Web of Science Index) and Obstetrics Gynecology (Web of Science Categories) and Article (Document Types)

RESULTS

General Characteristics and Global Productivity

On September 1, 2022, articles were queried from the Wos Core Collection's SCIE index. A total of 2252 documents were discovered, and we then narrowed the search results to original articles only from obstetric and gynecology research area. We found a total of 993 articles according to the search criteria. 12.79% of the articles were published as open access and 96.375% of them were in English. 57% of the articles published since 2010.

These articles had a Hirsch (h)-index of 70, a total of 23538 citations, and an average of 23.7 citations per article. Although the number of publications about LH changes from year to year, it peaked in 2015 (number of publications was 59) and it had the highest citation numbers (n=1800) in 2021 (**Figure 1**). The published articles were evaluated in the WoS database for country-base productivity. We discovered that the most productive country, with 289 articles, was the USA, and 51 countries contributed to the LH literature. In other words, the USA, Italy, Germany, South Korea, Australia, France, Taiwan, Turkey, England, and China were the top leading countries in the ranking of mostly publishing countries on LH, and the majority of the articles included in our analysis were published in America and Europe (**Figure 2**).

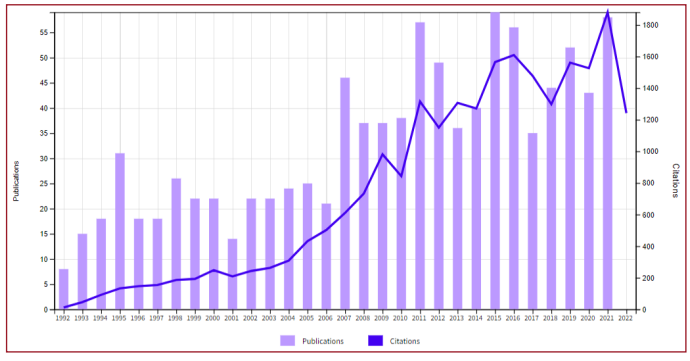

Figure 1. Graph of laparoscopic hysterectomy publications and citations since 1992

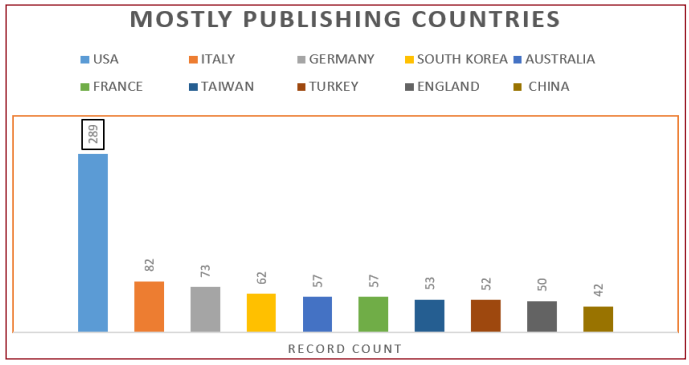

Figure 2. The top ten publishing country rankings on laparoscopic hysterectomy

Authors' and Institutions' Productivity and funding agencies

Our findings show that throughout the research period, 3448 authors contributed to the publication of scholarly works on LH. Prof. Fabio Ghezzi from the University of Insubria (Italy) was the most published author on LH with 25 articles. Prof. Fabio Ghezzi's articles on LH were cited 735 times (29.4 per article). Most of the articles were published from affiliations located in Italy and the USA (**Table 1**).

Table 1. The list of mostly publishing affiliations on laparoscopic hysterectomy.

Affiliations, country	n	%
University of Insubria, Italy	29	2.920
Udice French Research Universities, France	28	2.820
Harvard University, USA	24	2.417
Assistance Publique–Hôpitaux de Paris, France	23	2.316
The University of Texas System, USA	22	2.216
The Linkou Chang Gung Memorial Hospital, Taiwan	21	2.115
Catholic University of the Sacred Heart, Italy	18	1.813
La Fondazione Policlinico Universitario Agostino Gemelli, Italy	18	1.813
Brigham and Women's Hospital, USA	16	1.611
The Cleveland Clinic Foundation, USA	16	1.611

*Showing 10 out of 1.130 entries:8 record(s) (0.806%) do not contain data in the field being analyzed

The United States Department of Health and Human Services was the main funding agency of the LH topic's articles (**Table 2**).

Table 2. The leading funding agencies of laparoscopic hysterectomy research.

Funding Agencies	n	%
United States Department of Health Human Services	29	2.920
National Institutes of Health	28	2.820
National Cancer Institute	14	1.410
National Natural Science Foundation of Guangdong Province	5	0.504
National Science And Technology Support Program of China	5	0.504
Eunice Kennedy Shriver National Institute of Child Health Human Development	5	0.504
National Center For Advancing Translational Sciences	5	0.504
National Natural Science Foundation of China	4	0.403
Science and Technology Plan of Guangzhou	4	0.403
Ethicon Endo Surgery Inc	3	0.302

*Showing 10 out of 181 entries; 862 record(s) (86.808%) do not contain data in the field being analyzed

Journals

The LH articles were mostly (n=189,19.033%) published in the Journal of Minimally Invasive Gynecology journal and 52 different journals published the LH articles (**Table 3**).

Table 3. The summary of the mostly publishing journals on laparoscopic hysterectomy

Journals	n	%	Journal Impact Factor ™ (five year)
The Journal of Minimally Invasive Gynecology	189	19.033	3.935
The Journal of the American Association of Gynecologic Laparoscopists	74	7.452	-
Archives of Gynecology and Obstetrics	65	6.546	2.804
Gynecologic Oncology	55	5.539	5.696
The European Journal of Obstetrics & Gynecology and Reproductive Biology	52	5.237	2.778
Obstetrics & Gynecology	46	4.632	7.767
American Journal of Obstetrics & Gynecology	43	4.330	9.491
The International Journal of Gynecological Cancer	39	3.927	
The Australian and New Zealand Journal of Obstetrics and Gynaecology	32	3.223	3.622
Acta Obstetricia et Gynecologica Scandinavica	28	2.820	4.334

Showing 10 out of 52 entries

A search on the Medline (Pubmed) database with the same keywords in the same timeframe yielded 5964 articles. Similarly, most of the articles on LH are published in the Journal of Minimally Invasive Gynecology (928 publications) (**Table 4**). But the Pubmed database has some limitations, such as the publications can not be divided into research area subgroups.

Table 4. The list of mostly publishing journals and citations according to Pubmed on laparoscopic hysterectomy between 1992-2021.

Name	Publications	Citations
Journal of Minimally Invasive Gynecology	928	17507
Gynecologic Oncology	210	12713
Obstetrics and Gynecology	185	10504
American Journal of Obstetrics and Gynecology	170	7378
JSLS Journal of the Society of Laparoscopic & Robotic Surgeons	165	3588
European Journal of Obstetrics & Gynecology and Reproductive Biology	150	3339
Archives of Gynecology and Obstetrics	131	2171
International Journal of Gynecological Cancer	128	3139
International Urogynecology Journal	112	2089
BJOG An International Journal of Obstetrics & Gynaecology	90	3865

VosViewer mapping

The average number of authors per paper over the research period was 0.287 (0.035) (standard error of the mean). Using VOSviewer, we generated a graphical representation of the network mapping of co-authorship between countries in **Figure 3**.

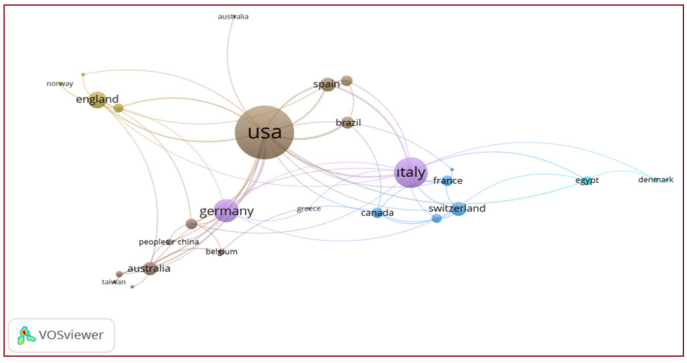

Figure 3. Co-authorship analysis among countries

International cooperation was defined as papers co-authored by authors from more than one country. **Figure 4** depicts the international collaborative network map. Using the VOS viewer technique, international collaboration analysis for active countries with at least one document revealed clusters of international collaboration. Lines connecting countries indicate cooperation. Stronger cooperation is indicated by thicker lines. Countries represented by larger circle or letter sizes have a higher level of international collaboration. The following countries are active in all world regions: the USA, Italy, France, South Korea, and Germany (**Figure 4**).

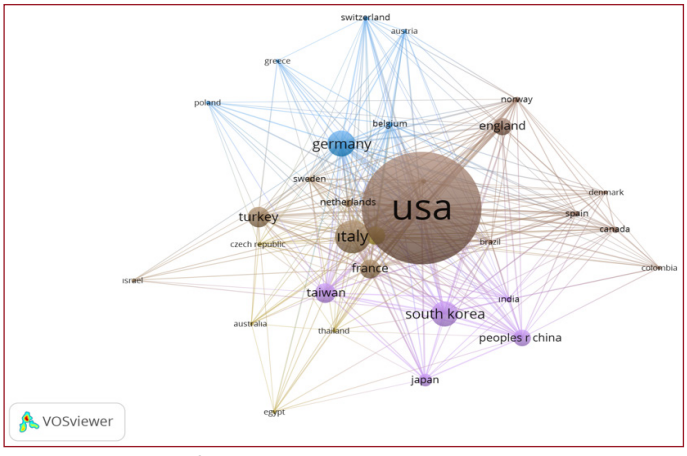

Figure 4. Citation analysis among countries

Figure 5 decipts the keyword analysis of the articles on LH.

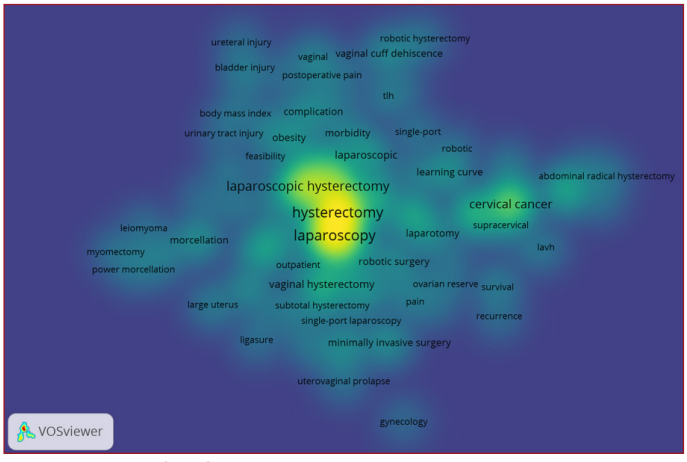

Figure 5. Keyword analysis

DISCUSSION

In bibliometric analysis, internet databases are widely utilized. While this method was commonly utilized in social field analyses in earlier years, it has recently been used in medicine, which is our field. In recent years, many different bibliometric analysis approaches have begun to enter the medical literature, and analysis research on this subject might be extended by methods like mapping and graphing. Many methodologies can be used to conduct these investigations, including content analysis, comparisons of scientific productivity by years, countries, and citation numbers. Databases that allow simple and comprehensive data analysis, such as Elsevier's Scopus, Medline/Pubmed, and Wos databases are often used for bibliometric studies. However, this method can be used to evaluate other sources such as any database, theses, journals, conferences, and so on.[21-31] However, no equivalent bibliometric analysis has been conducted on LH. As a result, we aimed to evaluate the evolution of the number of publications and citations over time, identify the most productive countries, academics, and journals, and guide future science. An international bibliometric analysis of LH articles from obstetrics and gynecology research areas throughout the course of 30 years was carried out for this study. Due to the lengthy duration and thoroughness of the bibliographic search, we were able to properly implement bibliometric techniques and indices to minimize data relativity to the greatest extent. The purpose of this study is to perform a bibliometric analysis on published publications on the topic of LH to ascertain their characteristics and trends. We located every original study on LH published between January 1992 and September 2022 using the Wos database. With the use of the software VOSviewer, bibliographic and citation data were gathered and collaborative networks of nations and keywords associated with LH were visualized. This bibliometric analysis highlighted the global research trends and developments, as well as the impact of the field on science and the interaction of researchers in the area of LH. The number of articles published on LH between 2010 and 2021 has a linear growth rate, which denotes growth that is consistent but unaffected by sample size and has not yet saturated. In terms of articles published, Prof. Fabio Ghezzi from the University of Insubria in Italy was the highest-ranking author. Also, our data suggest that 3448 authors from 51 countries contributed to the publishing of scholarly papers on LH throughout the research period, and this information shows the global importance of the issue.

It is determined that the journal with the highest number of documents is "The Journal of Minimally Invasive Gynecology". This journal's five-year impact factor was 3.935. It is understood that the journals with the highest number of documents on LH have a high impact factor. And also, in our study, we only selected the articles published in SCIE.

Our keyword analysis results state that LH is the preferred keyword in bladder surgery, uterus surgery, and even cancer surgery topics. Our keyword analysis results can help those who will do research on this subject.

Limitations

There are some limitations to this study. The first is that our field of study is only one discipline, so thorough evaluations and comparisons are impossible. Another limitation is that, while the Web of Science, the database used in our analysis, contains the most valuable documents published, it does not cover all of the articles on the subject. As a result, no documents published anywhere in the world were considered.

CONCLUSION

The number of articles published on this topic has skyrocketed in recent times. This increase in the number of published articles and citations suggests that the subject will become more popular in the next few years. As a result of our analysis, clinicians and researchers will be able to readily detect which articles about LH are popular and which themes are more cited as a result of our analysis. We anticipate that our findings will serve as a model for future research on LH for the obstetric and gynecology fields. The results of this study may offer obstetricians and researchers insight into global obstetric research and may also assist policymakers in assessing the performance of scientists doing research both domestically and internationally.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval as it is a study on articles not received. Ethics committee approval is not required as there is no human or animal research.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that he has all participated in the design, execution, and analysis of the paper, and that he has approved the final version.

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Original Article / Orijinal Araştırma

Retrospective Investigation of HBsAg and Anti-HCV Seroprevalence in Patients Admitted at the Outpatient Clinics of Internal Medicine

Dahiliye Polikliniğine Başvuran Hastalarda HBsAg ve Anti-HCV Seroprevalansının Retrospektif Olarak Araştırılması

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Abstract

Aim: Hepatitis B and Hepatitis C viruses are among the viral hepatitis agents and constitute an important public health problem as they can cause serious complications. Patients examined at outpatient internal medicine clinics are among the main risk groups, as they have concomitant diseases and undergo various procedures. In this study, we aimed to retrospectively investigate the seroprevalence of HBsAg and Anti-HCV in outpatients in internal medicine in our region.

Material and Methods: HBsAg and Anti-HCV parameters of the patients admitted to our hospital's internal medicine outpatient clinics between January 2017 and July 2022 are evaluated. Then, HBV-DNA and HCV-RNA levels of the patients who were found to be reactive in these parameters and demographic data such as age and gender were examined retrospectively.

Results: In this study, HBsAg test results of 2618 patients and Anti-HCV test results of 2943 patients were obtained. The mean age of patients with HBsAg tests was 34.2±15.7, and the mean age of patients with Anti-HCV tests was 34.3±15.7 years. The HBsAg reactivity rate was 0.9%; and the mean age of patients showing reactivity was 47.7±14.4 years. The Anti-HCV reactivity rate was %0.1, with a mean age of 52.6±21.3 years. Neither HBsAg nor Anti-HCV reactivity was not present in the same patient in our study.

Conclusion: The early detection of Hepatitis B and Hepatitis C viruses is crucial in reducing the risk of developing complications, simplifying the treatment process, and decreasing the likelihood of transmission. As a result, the implementation of screening tests as a component of preventive medicine is of utmost importance.

Keywords: HBV infection, HCV infection, seroprevalence

Öz

Amaç: Viral hepatit etkenleri arasında yer alan Hepatit B ve Hepatit C virüsleri ciddi komplikasyonlara neden olabildikleri için önemli bir halk sağlığı sorunu oluşturmaktadır. Dahiliye polikliniklerine başvuran hastalar eşlik eden hastalıklar ve uygulanan işlemler nedeniyle başlıca risk grupları arasındadır. Biz bu çalışmayla bölgemizde dahiliye polikliniklerine başvuran hastalarda HBsAg ve Anti-HCV seroprevalansını retrospektif olarak incelemeyi amaçladık.

Gereç ve Yöntem: Ocak 2017-Temmuz 2022 tarihleri arasında hastanemiz dahiliye polikliniklerine başvuran hastaların HBsAg ve Anti-HCV parametreleri, bu parametrelerinde reaktiflik saptanan hastaların HBV-DNA ve HCV-RNA düzeyleri, yaş ve cinsiyet gibi demografik verileri retrospektif olarak değerlendirildi.

Bulgular: Çalışmada 2618 hastanın HBsAg, 2943 hastanın ise Anti-HCV test sonuçları elde edildi. HBsAg çalışılan hastaların yaş ortalaması 34.2±15.7 iken Anti-HCV çalışılan hastaların yaş ortalaması ise 34.3±15.7 olarak bulundu. HBsAg reaktifliği oranı %0.9 saptandı; reaktiflik belirlenen hastaların yaş ortalaması 47.7±14.4 olarak bulundu. Anti-HCV reaktifliği oranı %0.1 gözlendi; reaktiflik saptanan hastaların yaş ortalaması 52.6±21.3 olarak belirlendi. Çalışmamızda HBsAg ve Anti-HCV reaktifliğinin birlikte görüldüğü hasta izlenmedi.

Sonuç: Hepatit B ve Hepatit C virüslerinin erken tanısı komplikasyon gelişim riskini azaltmakta, tedavi süreçlerini kolaylaştırmakta ve bulaş riskini düşürmektedir. Bu sebeple koruyucu hekimlik kapsamında tarama testlerinin yaygınlaşması oldukça önemlidir.

Anahtar Sözcükler: HBV enfeksiyonu, HCV enfeksiyonu, seroprevalans

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INTRODUCTION

Viral hepatitis infections impose a critical global public health problem due to severe complications such as chronic hepatitis, hepatic cirrhosis, and hepatocellular carcinoma. Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are among the leading causes of acute and chronic viral hepatitis agents.[1]

Approximately a third of the world population is reported to have contracted HBV infection previously, 250.000 people are reported to be infected chronically, and 887.000 patients were lost due to complications of HBV infection in 2015.[1-4] Turkey is considered to be among the moderately endemic countries with regard to the HBV seroprevalence, with a range of 2-4%.[3,5]

It is estimated that over 70 million individuals globally are living with chronic HCV infections, and in 2015, there were approximately 1.75 million newly reported cases of HCV infections.[1,2] Turkey is reported to be in the 1.0-1.9% zone regarding HCV seroprevalence. In addition, approximately 250.000-550.000 persons are thought to be infected with HCV among the population older than 18 years.[1,4,6]

The predominant modes of transmission for HBV and HCV vary across countries and regions.[1,2] Patient populations that are identified to have an increased risk of contracting viral hepatitis include individuals undergoing hemodialysis, those who frequently receive blood or blood product transfusions, patients with cancer, and those undergoing invasive procedures.[1,2,7] While HBV infection is a preventable disease due to the hepatitis B vaccine, there is no vaccine yet for hepatitis C infection.[1] HBV vaccine was incorporated into the national vaccination calendar in 1998.[8]

The objective of our study was to retrospectively evaluate the seroprevalence of HBsAg and Anti-HCV in outpatients visiting the internal medicine clinics. We aimed to examine the demographic distribution of these infections in our region by analyzing the data of patients based on their age and gender. Despite the significant progress made in the prevention and vaccination against HBV in our country, viral infections continue to be a critical public health issue. Hence, it is crucial to understand the prevalence of these infections in our region to take effective preventive measures.

MATERIAL AND METHOD

Following approval from the local ethics committee (2022/89, dated 08/10/2022), the study was initiated. The seroprevalence of HBsAg and Anti-HCV in patients admitted to the outpatient clinics of internal medicine was retrospectively investigated. Demographic information such as age and gender was also analyzed. The study was conducted by reviewing medical records of patients who visited the outpatient clinics of internal medicine at our hospital for various reasons between January 2017 and July 2022. For patients who tested positive for HBsAg and/or Anti-HCV, additional tests for HBV-DNA and HCV-RNA levels were performed. Repeat results, patients with foreign nationality, and infants were excluded from the analysis.

HBsAg and Anti-HCV tests were done with i1000SR analyzer (Abbott Diagnostics Division, Germany). In the interpretation for HBsAg and Anti-HCV reactivity, a level of 1.0 mIU/mL was accepted as a reference, following the producer's recommendation.

A real-time PCR method was performed for the detection of HBV-DNA and HCV-RNA by using the manufacturer's system (Anatolia Geneworks, Turkey).

Statistical analysis

The data obtained in the study were analyzed by SPSS 22.0 (SPSS INC, Chicago, IL, USA). Categorical variables were given as a percentage and mean±standard deviation. The Chi-square test was used to compare independent groups with categorical variables. The p-value <0.05 was considered statistically significant.

RESULTS

HBsAg results of 2618 patients and Anti-HCV test results of 2943 patients were evaluated during the study period. 1827 (69.8%) patients with HBsAg results were female; while 2058 (69.9%) patients with Anti-HCV results were female. The mean age of patients with HBsAg results was 34.2±15.7 years (18-89) and mean age of patients with Anti-HCV results was 34.3±15.7 years (18-92).

HBsAg reactivity was detected in 24 patients (0.9%) (**Table 1**). Mean age of these patients was 47.7±14.4 years (22-77). Twelve patients were (50.0%) female. The distribution of HBsAg reactivity status by age groups is shown in **Table 2**. The highest rate of positivity rate was found in the age range of 46-60 years (p <0.001). HBsAg values were between 39.5-6451.0 mIU/mL (4162.6±1550.6). HBV-DNA results were found for 12 patients whose HBsAg values were 39.5-6451.0 mIU/mL (3602.0±1815.7), and whose ages were between 25-77 years (46.8±14.1). Out of the 12 patients, ten had HBV-DNA levels between 102-107 IU/mL and followed up without treatment. The remaining patients had negative HBV-DNA results and were given antiviral treatment (tenofovir and entecavir) with follow-up.

Anti-HCV reactivity was detected in five patients (0.1%) (**Table 1**). The mean age of these patients was 52.6±21.3 years (27-85). All five patients were female. The distribution of anti-HCV reactivity status by age groups is shown in **Table 2**. The highest rate of positivity was observed in patients over 80 years of age (p <0.001). Anti-HCV values were between 1.4-35.9 mIU/mL (12.7±13.9). All five patients took antiviral medications (sofosbuvir, ledipasvir and ribavirin) and followed-up. The mean Anti-HCV values of treated patients decreased from 12.7±13.9 mIU/mL to 1.2±1.1 mIU/mL. In our study, no patient with both HBsAg and Anti-HCV reactivity was found.

Table 1: HBV and HCV serological test results

HBV serological test results	Numbers (n:2618)	%
HBsAg(+)	24	0.9
HBsAg(-)	2594	99.1
HCV serological test results	**Numbers (n:2943)**	**%**
Anti-HCV(+)	5	0.1
Anti-HCV(-)	2938	99.9

Table 2: Distribution of HBsAg and Anti-HCV reactive status according to age structure

	18-30 age n (%)	31-45 age n (%)	46-60 age n (%)	61-80 age n (%)	>80 age n (%)	p
HBsAg reactivity/ Number of patients studied	2/1379 (0.1)	8/691 (1.2)	9/106 (8.5)	5/222 (2.3)	0/220 (-)	<0.001
Anti-HCV reactivity/ Number of patients studied	1/1565 (0.1)	1/756 (0.1)	2/335 (0.6)	0/257 (-)	1/30 (3.3)	<0.001

DISCUSSION

Globally, viral hepatitis represents a significant challenge to public health due to its association with mortality, chronic illness, and economic losses. Despite the implementation of vaccination programs for hepatitis B virus (HBV) and improvements in living standards and public awareness, infections caused by HBV and hepatitis C virus (HCV) remain a major concern among infectious diseases.[8,9]

In recent studies conducted in Turkey, HBsAg seroprevalence was found between 0.3-4.0%, and Anti-HCV seroprevalence between 0.3-1.3%, respectively.[3,10-16] HBsAg and Anti-HCV seroprevalence was 2.5% and 0.9% in oncology patients and 1.0% and 0.8% in patients admitted at the outpatient clinics of family physicians in a tertiary care hospital in Karabük.[4,7] HBsAg and Anti-HCV reactivities were 1.5% and 0.1% in the preoperative evaluation of the patients in a private hospital in Van.[17] In a study in a tertiary care hospital in Niğde, where all patients in whom hepatitis markers were evaluated, HBsAg and Anti-HCV seroprevalences were respectively 4.0% and 1.2% in the general population, 0.04% and 0.04% in patients younger than 20 years, and 4.2% and 1.2% in patients older than 20 years.[18]

In light of the findings of our study, it can be concluded that the expanded implementation of HBV vaccinations and heightened social awareness have had a positive impact. Our study also found that seropositivity for HBsAg and anti-HCV was higher among patients aged 45 and older when compared to other age groups. However, it should be noted that the limited sample size of our data may have influenced the results.

In other studies conducted in our region, HBsAg and Anti-HCV seroprevalence were respectively 1.0% and 0.3% in preoperatively evaluated patients and 2.0% and 0.9% in patients hospitalized in intensive care units.[19,20] In a study where children born after the vaccination program was investigated, HBsAg reactivity was reported as 0.3%.[3] We found HBsAg seroprevalence as 0.9%, and Anti-HCV seroprevalence 0.1% in the present study. Factors such as study year, hospital (secondary or tertiary care) and hospital location (central or rural hospitals), and demographic characteristics of the study population may affect the results in seroprevalence studies. Our study was conducted in a secondary care rural state hospital. Patients generally prefer tertiary care hospitals located at the city center for diagnosis and treatment. For this reason, our results are consistent with existing medical literature, although the values obtained are slightly lower. We anticipate that the prevalence of HBsAg reactivity will continue to decrease in the future due to the inclusion of HBV vaccination in the national immunization schedule since 1998.

In a large-scale study at a tertiary care hospital in İzmir, Anti-HCV reactivity was 1.6%. The co-existence of Anti-HCV and HCV-RNA was also investigated in the study. Anti-HCV reactivity/HCV-RNA positivity was found in 7.0% of the patients, while Anti-HCV reactivity/HCV-RNA negativity was detected in 32.0%.[21] In our study, HCV-RNA was also found positive in all patients with anti-HCV reactivity. It is well recognized that the anti-HCV test is a screening test and may produce false-positive results as its sensitivity increases. As such, further evaluation using HCV-RNA testing is necessary when anti-HCV reactivity is detected. Improving screening methods for the detection of patients positive for HBV and HCV is also important. As screening methods become more widespread, the diagnosis and treatment of these diseases will become easier. Particular caution is advised for individuals in high-risk groups, such as dialysis patients, immune-compromised individuals, individuals with multiple sexual partners, sex workers, intravenous substance users, patients receiving frequent blood transfusions or blood product transfusions, and healthcare workers.

The limitations of our study include its retrospective design, the relatively small sample size, and the lack of access to other screening tests for HBV.

CONCLUSION

Infections caused by HBV and HCV pose a significant threat to public health. Early detection of these infections prior to the development of complications such as cirrhosis or hepatocellular carcinoma improves the prospects for successful treatment and reduces the risk of virus transmission. As such, HBsAg and anti-HCV tests play a crucial role in screening for these infections. The literature includes a study that similarly investigated the seroprevalence of HBsAg and anti-HCV in Balıkesir. A comparison of positivity rates highlights the influence of various factors on seropositivity. In the interest of preventive medicine, it is recommended that screening tests for HBV and HCV become more widespread and that every healthcare center maintain records of the HBsAg and anti-HCV positivity rates among its patient population.

ETHICAL DECLARATIONS

Ethics Committee Approval: Permission for this study was obtained from Balıkesir University Ethics Committee (Date: 10/08/2022, Decision No: 2022/89)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article / Orijinal Araştırma

Comparison of Urine Cultures of Home Care and Palliative Care Patients; Cross-sectional Study

Evde Bakım ve Palyatif Bakım Hastalarının İdrar Kültürlerinin Karşılaştırılması; Kesitsel Çalışma

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Abstract

Aim: Urinary tract infections (UTI) are an important cause of mortality, especially in geriatric patients. The effectiveness of urine culture and appropriate antibiotic use in geriatric patients followed in primary care is important. We aimed to compare the urine cultures and antibiotic susceptibilities of patients over 65 years of age with urinary system infections, who continue to be treated at home by the Home Care Services (HCS) and those in the Palliative Care Service (PCS).

Material and Method: Between January 1, 2019 and January 1, 2020, the culture-antibiogram results of the urine samples of patients aged 65 years and older with urinary infection complaints and followed and treated by PBS and HCS were compared retrospectively.

Results: Of the 60 patients included in the study, 30 had PCS, 30 HCS patients had a mean age of 78.0±12.7 years, and PCS patients had a mean age of 80.7±9.8 years. According to the culture-antibiogram results of the urine samples of the patients, *E. coli* was the most common microorganism in both groups (p=0.003). When we look at the antibiotic sensitivity of the patients in the HCS group, Amikacin (96.7%), Cefoxitin (83.3%), Fosfomycin (73.3%), Nitrofurantoin (70%) sensitive and Ampicillin (76.7%), Cefuroxime (36%), Ceftazidime (40%) was found resistant to Ciprofloxacin (33%). PCS group is sensitive to Amikacin (60%), Cefoxitin (23.3%), Fosfomycin (23.3%), Nitrofurantoin (16.6%) and Ampicillin (40%), Cefuroxime (26.7%), Ceftazidime (33.3% were found to be resistant to Ciprofloxacin (53.3%). In both groups, the highest resistance rates were found in Ampicillin, 76.7% in HCS patients and 40% in PCS patients, and the highest sensitivity rates were in Amikacin, 96.7% in HCS and 60% in PCS.

Conclusion: Antibiotic resistance status of bacteria should be considered. Care should be taken in the selection of antibiotics in accordance with rational antibiotic principles, and treatment management planning should be done in the right time with the right drug, the right dose, the right application method.

Keywords: Geriatrics, home care, pallative care

Öz

Amaç: Üriner sistem infeksiyonları (USİ) özellikle geriatrik hastalarda önemli bir mortalite nedenidir. Birinci basamakta takip edilen geriatrik hastalarda idrar kültürü kullanımının uygun antibiyotik kullanımı etkinliği önemlidir. Evde Bakım Hizmetleri (EBH) tarafından evde tedavisine devam edilen 65 yaş üstü üriner sistem enfeksiyonu hastaların ve Palyatif Bakım Servisi (PBS)'nde yatan hastaların idrar kültürlerini ve antibiyotik duyarlılıklarını karşılaştırmayı amaçladık.

Gereç ve Yöntem: 1 Ocak 2019 – 1 Ocak 2020 tarihleri arasında Üriner enfeksiyon şikayetleri olan 65 yaş ve üstü PBS ve EBH tarafından takip ve tedavi edilen hastaların idrar örneğinin kültür-antibiyogram sonuçları retrospektif olarak karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 60 hastanın 30'u PBS, 30'u EBH hastalarının yaş ortalaması 78,0±12,7 ve PBS hastalarının yaş ortalaması 80,7±9,8 idi. Hastaların idrar örneklerinin kültür-antibiyogram sonuçlarına göre her 2 grupta da en sık rastlanan mikroorganizmanın *E. coli* olduğu görüldü (p=0,003). Hastaların antibiyotik duyarlılığına baktığımızda EBH grubunda Amikasin(%96,7), Cefoxitin (%83,3), Fosfomisin (%73,3), Nitrofurantoin (%70)'e duyarlı ve Ampisilin (%76,7) Cefuroxime (%36,7) Ceftazidime (%40) Ciprofloxacin (%33)'e dirençli bulundu. PBS grubu Amikasin (%60), Cefoxitin (%23,3), Fosfomisin (%23,3), Nitrofurantoin (%16,6)'e duyarlı ve Ampisilin (%40), Cefuroxime (%26,7), Ceftazidime(%33,3), Ciprofloxacin (%53,3)'e dirençli olduğu bulunmuştur. Her iki grupta da en yüksek direnç oranları EBH hastalarında %76,7, PBS hastalarında %40 olmak üzere Ampisilin olarak ve en yüksek duyarlılık oranlarının ise EBH'de %96,7, PBS'de %60 olmak üzere Amikasin'de olduğu bulunmuştur.

Sonuç: Akılcı antibiyotik ilkeleri doğrultusunda antibiyotik seçiminde dikkatli olunmalı, doğru zamanda, doğru ilaç, doğru doz, doğru uygulama yöntemi ile tedavi yönetim planlaması yapılmalıdır.

Anahtar Kelimeler: Geriatri, evde bakım, palyatif bakım

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INTRODUCTION

Physiological and morphological changes cause elderly and frail patients to become more vulnerable to infections.[1] Urinary system infection (UTI) often causes different clinical pictures ranging from asymptomatic bacteriuria that does not require treatment to life-threatening urosepsis.[2] In elderly and frail patients, factors such as insufficient fluid consumption, inactivity, urinary incontinence, and infected area in the perianal region increase the risk of UTI development.[1] Frail elderly patients, who are associated with various disabilities such as a series of physiological and morphological changes, urinary incontinence, immobility and cognitive impairment, are at particularly high risk for the development of UTI.[3] It is important to diagnose and appropriately treat these infections in the elderly.[4]

For this purpose, antimicrobial resistance studies and literature information in this field can help in the selection of the appropriate antibiotic to be used in the treatment. Because of UTI, which is the most common cause of antibiotic use in the elderly and fragile population, long-term and insufficient dosage of antibiotics can lead to the formation of antibacterial resistance and most importantly the development of resistant organisms.[4-5] The success of the treatment may vary depending on the infectious agent and the appropriate antibiotic.[5] It is important to be aware of it in terms of both good diagnosis and prevention in order to avoid negative consequences.[4]

In the aging process, which concerns the whole of our society, home care services have become a service mostly used by individuals over the age of 65 with chronic diseases.[6] Palliative care (PC) With increasing age and treatments for cancer and other chronic diseases, the need for PC at the population level is significant.[7] For this reason, we aimed to compare the causes of urinary system infection, urine cultures results and antibiotic susceptibility, of those over 65 years of age who continue to be treated and followed up in their own home by HCS and inpatient treatment in PCS.

MATERIAL AND METHOD

The study was carried out with the permission of Giresun University Faculty of Medicine Ethics Committee (Date: 22/09/2020, Decision No: KAEK-05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The culture-antibiogram results of the urine samples of 60 patients who had urinary system infection complaints in PCS and HCS and were followed up and treated with UTI findings between 1 January 2019 and 1 January 2020 at Prof. Dr. A. İlhan Özdemir Training and Research Hospital were evaluated retrospectively. The detection of infection at the level of infection (105 cfu/ml) in the microbiology laboratories of Prof. Dr. A. İlhan Özdemir Training and Research Hospital was considered significant for urinary tract infection. Samples were seeded on 5% blood agar and Eosin Methylene Blue agar media. The media were incubated for 24-48 hours at 37°C under aerobic conditions. The number of growing colonies was expressed as CFU/ml. In addition to classical bacteriological methods, identification and antimicrobial susceptibility of the growing isolates were studied with the automated Vitek version 2.0 system (Biomerieux, France). Data Statistical analyzes were performed with IBM SPSS V23 (Chicago, USA). The number of samples to be taken in each group according to 95% confidence (1-α), 80% test power (1-β) and d=0.5 effect size one-tailed independent samples t test analysis using the G*Power program It is set to 30. Cases were numbered according to their file numbers, and the participants to be included in the study were assigned using a free internet-based random number generator (https://www.random.org) so that the number of patients in the groups was the same. Qualitative data were compared with the Pearson Chi-square test, and statistical significance was accepted as $p<0.05$.

RESULTS

Of the 60 patients included in the study, 30 were PCS and 30 were HCS followed and treated. While the mean age of the HCS group was78.0±12.7 the mean age of the PCS group was A 80.7±9.8 total of 21 male and 39 female patients were included in the study. When the sub-diseases were examined, it was found that the most common disease in both home care and palliative groups was cerebrovascular events. According to the culture-antibiogram results of the urine samples of the patients, *E. coli* was the most common urinary tract infection agent in both groups (**Table 1**)

Table:1 Descriptive Statistics

Microorganisms	Home Care (%)	Palliative Care (%)
E. coli	13(43.3)	6(20)
Proteus mirabilis	6(20)	2(6.7)
Klebsiella pneumoniae	8(26.7)	4(13.3)
Pseudomonas aeruginosa	2(6.7)	4(13.3)
Acinetobacter baumannii	1(3.3)	0
Candida albicans	0	5(16.7)
Enterecoccus faecalis	0	3(10)
Non Albicans Candida	0	4(13.3)
Providencia stuartii	0	1(3.3)
Serratia spp	0	1(3.3)

When microorganisms were compared according to resistance classification, it was seen that the most common microorganism Multi Drug Resistant (MDR) group was *Klebsiella pneumoniae* and Extensively Drug Resistant (EDR) *E. coli* was the most common microorganism.The microorganism encountered in the non-resistant group is *Candida albicans*. ($p<0.001$) (**Table 2**).

When the antibiotic resistances of the patients were compared with the microorganisms, it was determined that ampicillin resistance differed significantly according to the microorganism and the highest resistance was in *E. coli* bacteria. ($p=0.043$). The most sensitive microorganism to cefepime was *Pseudomonas aeruginosa* ($p=0.014$), while the most resistant microorganism to Ceftazidime was *E. coli* ($p=0.034$). *E. coli* was found to be

the most sensitive microorganism to imipenem (p=0.013) and Gentamicin (p=0.007). The most susceptible microorganism was *E. coli*, while the most susceptible microorganism was *Klebsiella pneumoniae* (p=0.001). The most sensitive microorganism to nitrofurantoin was *E. coli*, while the most resistant microorganism was *Proteus mirabilis* (p<0.001). Cefuroxime, cefoxitin, cefixime, ceftazidime, ceftriaxone, ertapenem, meropenem, amikacin, resistance status did not differ significantly according to the microorganism (p>0. 05) (**Table 3**)

Table 2: Comparison of Microorganisms by Resistance Classification

Mikroorganisms	Resistance Classification			p
	MDR(%)	EDR(%)	Non-resistant(%)	
Escherichia coli	3(15)	15(55.6)	1(7.7)	<0.001*
Proteus mirabilis	4(20)	4(14.8)	0	
Klebsiella pneumoniae	7(35)	5(18.5)	0	
Pseudomonas aeruginosa	3(15)	0	3(23.1)	
Acinetobacter baumannii	0	1(3,7)	0	
Candida albicans	0	0	5(38.5)	
Enterecoccus faecalis	2(10)	1(3.7)	0	
Non-albicans *Candida albicans*	0	0	4(3.8)	
Providencia stuartii	0	1(3.7)	0	
Serratia spp	1(5)	0	0	

*Fisher's Exact Test, MDR group (Multi Drug Resistant),EDR(Extensively Drug Resistant)

Table 3: Antibiotic resistances

Antibiotics		*E. coli* (%)	*Proteus mirabilis* (%)	*Klebsiella pneumoniae* (%)	p
Ampisilin	Sensitive	3(16,7)	0	0	0,043*
	Resistant	15(83,3)	7(100)	11(100)	
Amok.Kla	Sensitive	9(75,0)	2(40,0)	5(100)	0,075
	Resistant	3(25,0)	3(60,0)	0	
Sefepim	Sensitive	0	1(50)	0	0,014*
	Resistant	2(100)	1(50)	2(100)	
Cefuroxime	Sensitive	7(38,9)	3(42,9)	8(72,7)	0,235
	Resistant	11(61,1)	4(57,1)	3(27,3)	
Cefoxitin	Sensitive	15(83,3)	7(100)	9(81,8)	0,721
	Resistant	3(16,7)	0	2(18,2)	
Sefixim	Sensitive	7(38,9)	3(42,9)	8(72,7)	0,235
	Resistant	11(61,1)	4(57,1)	3(27,3)	
Ceftazidime	Sensitive	7(36,8)	4(50,0)	8(66,7)	0,034*
	Resistant	12(63,2)	4(50,0)	4(33,3)	
Ceftriaxone	Sensitive	7(38,9)	3(42,9)	8(72,7)	0,235
	Resistant	11(61,1)	4(57,1)	3(27,3)	
Ertapenem	Sensitive	17(94,4)	7(100)	9(81,8)	0,467
	Resistant	1(5,6)	0	2(18,2)	
İmipenem	Sensitive	19(100)	4(57,1)	9(81,8)	0,013*
	Resistant	0	3(42,9)	2(18,2)	
Meropenem	Sensitive	18(94,7)	8(100)	9(75,0)	0,108
	Resistant	1(5,3)	0	3(25,0)	
Amikasin	Sensitive	19(100)	8(100)	12(100)	0,062
	Resistant	0	0	0	

*p<0,05 Differences at the level of significance are statistically significant

DISCUSSION

Today, the increase in the elderly population and the health problems that may develop due to aging are increasing.[8] In this study; Bacteria and resistance profiles isolated from urinary tract infections in patients aged 65 and over were evaluated retrospectively according to the data of patients treated at home and treated in the palliative service.

The most common agents of urinary tract infections in the literature are *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter* spp. They have been reported as members of the *Enterobacteriaceae* family.[5] Similarly, in this study, the most isolated bacteria from the sample from the types, respectively; *Escherichia coli*, *Klebsiella* spp, from the *Enterobacteriaceae* family and *Proteus mirabilis*. These microorganisms *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Acinetobacter baumannii* were found as isolates.

According to the results of the retrospective analysis performed in our study, the most common microorganism in HCS (43.3%) and PCS (20%) wards was *E. coli*. The results show that *E. coli* species are highly responsible for community-acquired UTI, similar to the literature. *Candida albicans* infections take the second place in PBS patients. The reason for this may be the weakness of the immune system and urinary catheterization of the hospitalized patients.The widespread use of antibiotics has led to increased resistance to them, which makes the treatment of infections more difficult in the future.[9] The most commonly prescribed drugs in the treatment of UTI in our country are amoxicillin, amoxicillin clavunate, cephalosporins and trimethoprim-sulfamethoxazole(TMP-SMX) the most common parenteral therapies are aminoglycosides and third generation cephalosporins. Amoxicillin, cefixime, nitrofurantoin, and TMP-SMX are used in prophylaxis.[10] Ampicillin resistance was found to be 68.9% and TMP-SMX resistance was 46.7% in Kömüroğlu et al. evaluation of all gram-negative microorganisms together, revealed the highest resistance against ampicillin (75.1%), cefazolin (59%), ampicillin-sulbactam (49.7%),TMP-SMX (45.2%), cefixim (33.1%) and ceftriaxone (31.4%). The lowest resistance was against meropenem (3.2%), ertapenem (3.4%), colistin (7.2%), amikacin (16.2%), ciprofloxacin (21.1%) and piperacillin tazobactam (23.2%).[10]

In a study, the antibiotics to which *E. coli* strains are most sensitive and their resistance rates are as follows; amikacin (0.4%), tigecycline (2%), imipenem (2%), and meropenem (2%). The resistance rates in the antibiotics with the highest resistance are respectively; sefixime (32%), seftriaxone (29%) and TMP-SMX (28%) were detected.[11] In a study conducted in Turkey, the highest rate of ampicillin resistance was found to be (61.4%).[12] In our study, ampicillin resistance was (76.7%) in HCS patients and (76.7%) in PCS patients.

In this study, a high sensitivity of (96.7%) in HCS and (60%) in PCS was found for amikacin. In a study conducted in Iran, it was reported that *E. coli* is fully susceptible to amikacin and tobramycin.[13]

Considering the cefuroxime sensitivity of the patients, it was observed that the patients in the HCS group were (50%) and (10%) in PCS. In Cefoxitin, sensitivity rates were higher than resistance in both groups. cefixime, ceftriaxone, ceftazidime *E. coli* strains isolated from HCS patients showed high sensitivity to cephalosporin group antibiotics, while the rate of resistance to cephalosporin group increased in PCS patients. Inappropriate treatments pave the way for resistance development and an increase in economic burden.[10]

In this study It was found that while it was (33%) in ciprofloxacine patients in the home health group, it was (53.3%) in patients receiving palliative care. We see an increase in the development of resistance, especially in hospitalized patients. We think that one of the aims of antibiotic management is to act selectively to reduce antibiotic resistance and to use it more carefully in order to reduce increased health costs and higher complication risks.

It was determined that there were no ertapenem-resistant patients in the HCS group, and (10%) of the patients in the PCS group were resistant. Elderly patients have a higher risk of developing uroseptic shock than younger patients. [14] Again, the percentage of patients resistant to imipenem was (13.3%), respectively, while it was (6.7%) in the other group. Sensitivity rate to gentamicin is (86.7%) in HCS and (50%) in PCS.

In a study, the lowest resistance rates in *E. coli* strains isolated were nitrofurantoin (12.7%) and fosfomycin. (2.7%) was reported to develop against it.[15] In This study the sensitivity to fosfomycin was (73.3%) in ESR, it was (23.3%) in PBS, while the sensitivity to nitrofurantoin was (70%)in HCS and (16.7%) in PCS. It can be thought that these two antibiotics may affect the treatment positively in urinary tract infections. In a study conducted in Italy, it was reported that there was a significant decrease in fosfomycin resistance from (52.94%) to (33.6%).[16]

When the differentiation of the antibiotic susceptibilities of the patients was examined, it was observed that there was a significant differentiation according to the groups in all antibiotics except aztreonam, colistin, netilmicin. tobramycin, vancomisin and linezolida. Greater attention should be paid to the diagnosis and treatment of UTIs that affect elderly patients, who constitute a particularly vulnerable patient population.[17]

Limitations

In our study are that it is a retrospective study, the number of patients included in the study is small, and risk factors such as underlying immunosuppression were not compared in these patient groups. However, the frequent occurrence of urinary infections in the geriatric population will increase the success of prevention and treatment, knowing the resistance profiles of the reproducing microorganisms.

CONCLUSION

Antibiotic resistance status of bacteria should be considered. Care should be taken in the selection of antibiotics in accordance with rational antibiotic principles, and treatment management planning should be done in the right time with the right drug, the right dose, the right application method.

ETHICAL DECLARATIONS

Ethics Committee Approval: Permission for this study was obtained from Giresun University Clinical Researches Ethics Committee (Date: 22.09.2020, Decision No: KAEK -05)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article / Orijinal Araştırma

The Effects of Health Literacy on Early Diagnosis Behaviors of Breast and Cervical Cancer in Women Aged 18-65

18-65 Yaş Arası Kadınlarda Sağlık Okuryazarlığının Meme ve Servis Kanserinin Erken Tanı Davranışlarına Etkisi

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Abstract

Aim: It is stated that the level of health literacy is related to preventive health services, and low level of health literacy prevents screening tests. This study aimed to determine the effect of health literacy level on early diagnosis behaviors of breast and cervical cancer in women between the ages of 18 and 65.

Material and Method: The descriptive and cross-sectional study was conducted with female patients who admitted to the Obstetrics and Gynecology Outpatient Clinics of a Training and Research Hospital in the Central Black Sea region. Data were collected using the Introductory Information Questionnaire prepared by the researcher and the European Health Literacy Scale (HLS-EU) between June 2019 and January 2020. The sample of the study included 395 women who were not pregnant, had not undergone hysterectomy, were between the ages of 18 and 65, were married or sexually active, had no psychiatric, hearing or visual impairments, and were not diagnosed with breast and cervical cancer before.

Results: 41.8% of women are between the ages of 18-34. 42.3% of women are graduates of higher education, 46.8% of them are not working. 91.9% of all women are married and 83.8% have a nuclear family. The mean general health literacy score of women on the HLS-EU is 32.43±7.36. 40.3% of women have a problematic-limited level of health literacy. In the study, a statistically significant relationship was determined between the general score of HLS-EU and the state of knowing Clinical Breast Examination (CBE) (p=0.027) gender of the doctor in CBE (p=0.019), having gynecological examination before (p=0.008), knowing Pap-smear test (p=0.027), having Pap-smear test before (p=0.044),

Conclusion: The level of health literacy of women is problematic- limited. It has been determined that breast and cervical cancer information and early screening practices are insufficient, and insufficient health literacy level prevents participation in cancer screenings.

Keywords: Breast cancer, health literacy, cervical cancer, nurse

Öz

Amaç: Bu araştırmanın amacı 18 ve 65 yaş arası kadınlarda sağlık okuryazarlığı düzeyinin meme ve serviks kanseri erken tanı davranışlarına etkisinin belirlenmesidir.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel türdeki araştırma, Orta Karadeniz bölgesinde yer alan bir Eğitim ve Araştırma Hastanesinin Doğum ve Kadın Hastalıkları Polikliniklerine başvuran kadın hastalar ile yürütülmüştür. Araştırma verileri Haziran 2019-Ocak 2020 tarihleri arasında araştırmacı tarafından hazırlanan Tanıtıcı Bilgiler Soru Formu ile Avrupa Sağlık Okuryazarlığı Ölçeği Türkçe formu (ASOY-TR) kullanılarak toplanmıştır. Araştırmanın örneklemine gebe olmayan, histerektomi geçirmemiş, 18 ve 65 yaş arasında olan, evli veya cinsel yönden aktif, psikiyatrik, işitme ve görme engeli olmayan, daha önce meme ve serviks kanseri tanısı almayan 395 kadın dahil edilmiştir.

Bulgular: Kadınların %70,1'i 25-44 yaş aralığındadır. Kadınların %42,3'ü yükseköğretim mezunudur, %46,8'i çalışmamaktadır. Tüm kadınların %91,9'u evlidir ve %83,8'i çekirdek aileye sahiptir. Kadınların Avrupa Sağlık Okuryazarlığı Ölçeği (ASOY- TR) genel sağlık okuryazarlığı puan ortalaması 32,43±7,36'dir. Kadınların %40,3'ü sorunlu- sınırlı sağlık okuryazarlığı düzeyine sahiptir. Araştırmada ASOY-TR genel puanı ortalaması ile Klinik Meme Muayenesi (KMM)'nin ne olduğunu bilme (p=0,027), tarama/ kontrol amaçlı KMM yaptırmada hekimin cinsiyetinin kadın olması (p= 0,019), jinekolojik muayene yaptırma durumu (p=0,008), Pap-smear testini bilme durumu (p=0,027), daha önce Pap-smear testi yaptırma durumu (p=0,044) arasında istatistiksel olarak anlamlı düzeyde bir ilişki belirlenmiştir.

Sonuç: Kadınların sağlık okuryazarlığı düzeyinin sorunlu- sınırlı düzeydedir. Meme ve serviks kanseri bilgi ve erken tarama uygulamalarının yetersiz olduğu, yetersiz sağlık okuryazarlığı düzeyinin kanser taramalarına katılımın engellediği belirlenmiştir.

Anahtar Kelimeler: Meme kanseri, sağlık okuryazarlığı, serviks kanseri, hemşire

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INTRODUCTION

There were an estimated 19.3 million new cancer cases and approximately ten million cancer-related deaths in 2020 worldwide. The most frequently diagnosed type of cancer in women is breast cancer and it is estimated that approximately 2.3 million people are newly diagnosed globally.[1] The most significant challenges encountered in breast cancer treatment are the inability to detect cancer at an early stage and the low awareness in women about the disease. Methods, such as Breast Self-Examination (BSE), Clinical Breast Examination (CBE) and mammography, are used in the early diagnosis and breast cancer treatment.[2-4] The national breast cancer screening program in Turkey provides counseling for monthly breast self-examination (BSE), clinical breast examination once a year and mammography every two years for women aged 40-69 years.[5]

Cervical cancer is a late-onset result of a sexually transmitted infection, Human Papillomavirus (HPV), and is cancer that can be prevented by vaccination and early screening.[6] In 2018, it was estimated that approximately 570,000 women worldwide were diagnosed with cervical cancer, and approximately 311,000 women died due to cervical cancer.[7] On the other hand, it is stated that 2532 women are diagnosed with cervical cancer every year and 1245 women die from cervical cancer in Turkey.[8] The first finding in the early diagnosis of cervical cancer is the abnormal result of the Pap smear test or HPV DNA test, which has become widespread in recent years.[7] The standard cervical cancer screening program in our country is for women in the 30-65 age group to have a Pap smear test every five years at the Early Diagnosis, Screening and Education Center of Cancer (KETEM).[5]

Today, individuals are expected to adopt behaviors that will protect and improve their health, benefit from the health services offered, be able to make decisions about their own health status, and be aware of their own responsibilities and rights. On the other hand, factors, such as constantly developing and changing technology, complexities encountered in the diagnosis process, cultural differences, limited health literacy and age affect the self-care and competence of individuals, the use of health services provided and their communication with health personnel. In this respect, health literacy is a significant step, and it facilitates the ability to search and understand health-related information and communicate with health care providers.[9]

The definition of health literacy made by World Health Organization (WHO) is "cognitive and social skills that describe the motivation and ability of people to access, understand and use the information to improve and maintain their health".[10] Studies have determined that there is a relationship between breast and cervical cancer screening behaviors and health literacy level.[11-17] It is stated that the level of health literacy of women affects their beliefs and behaviors in cancer prevention.[18] When the relationship between health literacy level and preventive health services is examined, it is stated that a low health literacy level prevents performing screening tests.[19] There are few published data on health literacy in Turkey, so the relationship between individuals' health literacy and cancer screening is significant.

MATERIAL AND METHOD

This descriptive and cross-sectional study aimed to determine the effect of health literacy level on early diagnosis behaviors of breast and cervical cancer in women between the ages of 18 and 65. This study was conducted with female patients who were admitted to the Obstetrics and Gynecology Outpatient Clinics a Training and Research Hospital, located in the Central Black Sea region of Turkey, between June 2019 and January 2020. The study population was female patients between the ages of 18-65.

Inclusion criteria for this study were not being pregnant, not having a history of total hysterectomy due to a benign tumor, being married or sexually active between the ages of 18 and 65, not having a psychiatric problem, hearing and visual impairment, and not having been diagnosed with breast and cervical cancer before. Oral and written consent was obtained from the patients before the interview, and then the data were collected with a 15-minute face-to-face interview in a private room before the examination.

The known universe sampling formula was used to determine the sample of this study. The present study was completed with 395 volunteer women who met the selection criteria according to the result obtained from the 'sampling with known universe' formula given below. In collecting research data, the 64-question Introductory Information Questionnaire prepared by the researcher and the European Health Literacy Scale (HLS-EU) Turkish version which Abacıgil, Harlak and Okay performed their Turkish validity and reliability study in 2016, were used.[20]

The questionnaire, which was prepared by reviewing the literature, consisted of the first part with 26 questions about sociodemographic characteristics (age, education, occupation, employment, income, marital status, place of residence, family type, duration of marriage (years), body mass index, smoking, alcohol use) and obstetric information (age at menarche, number of pregnancies, age at first birth, last birth type, number of children, duration of breastfeeding, use of contraception, duration of contraceptive pill use, presence of Sexually transmitted infections (STIs), menopause, menopausal age, using of Menopaual Hormone therapy (MHT), the second part with 20 questions about early diagnosis behaviors of breast and cervical cancer (knowing what BSE is, knowing how to do BSE, performing BSE, frequency of performing BSE, time of performing BSE, knowing what CBE is, status of having CBE, frequency of having CBE administered, knowing what mammography is, status of having mammography,

frequency of having mammography, having gynecological examination for screening/control, frequency of gynecological examination, knowing what Pap-Smear test is, previous Pap-Smear status, Pap-Smear test frequency, knowing what HPV vaccine is, doing HPV vaccination, consideration of getting the HPV vaccine to their children) and the third part with 18 questions about early diagnosis behaviors of cervical cancer.

European Health Literacy Scale (HLS-EU)

European Health Literacy Scale (HLS-EU), which was adapted into Turkish with the Turkish Health Literacy Scales Reliability and Validity Study, is the Turkish version of the European Health Literacy Scale. The scale was developed by the European Health Literacy Research Consortium (HLS-EU Consortium, 2012). The scale is a self-report scale developed to assess health literacy in people over the age of 15. This scale includes three health-related dimensions as treatment, prevention of diseases and health promotion, and four information-acquisition processes about health-related decision-making and practices, including reaching, understanding, decision-making and application. The scale consists of 3 sub-dimensions and 47 items. Each item is rated as 1= 'Very difficult', 2= Difficult, 3= 'Easy', 4= 'Very easy'. Code 5 is used for the expression "I don't know". Those who tick 'I don't know' will not be given points. Each participant can mark only one option from the five-point Likert scale. The total score that can be obtained from the scale is between 47-188. For ease of calculation, the total score is calculated using the formula, with a range of 0-50. According to the score obtained, cut-off points were determined for four dimensions (general treatment, prevention of diseases, and health promotion). If the health literacy level is between 0-25 points, it is classified as insufficient Health Literacy, if it is between 25-33 points, it is classified as problematic-limited Health Literacy, if it is between 33-42 points, it is adequate Health Literacy, and between 42-50 points it is classified as perfect Health Literacy. The Cronbach's alpha value of the scale is 0.95.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 was used to evaluate the data in this study. Descriptive statistics were shown as number (n), percent (%) and mean ± standard deviation (X±SD). The Kolmogorov-Smirnov test was used to examine the normality distribution of the scale mean scores. In line with the results obtained, the Chi-Square test was performed. The results were evaluated at a 95.0% confidence interval, $p<0.05$ significance level and $p<0.01$ and $p<0.001$ advanced significance level.

Ethical Approval

This study was conducted in accordance with the Principles of Helsinki and ethical approval was obtained from the non-interventional ethics committee of Hitit University (Date: 28.03.2019, Number: 2019-116).

RESULTS

In **Table 1**, the distribution of the descriptive characteristics of the women participating in this research is given. The mean age of the women participating was 37.26± 9.91, and 41.8% of the women were in the 18-34 age range. When the education level of women was examined, it was seen that 42.3% of them were university graduates and above, and 31.6% of them were primary school graduates. Almost half of the women in the study were not working and were housewives (51.4%). While 83.8% of women had a nuclear family, 71.9% perceived their income as a sufficient, and 59% live in rural ares, district or villages. In the study 91.9% of the women were married and the average duration of marriage was 14.13± 11.14 years, and 62.5% of them were married for 1-19 years. The mean BMI of the women was 25.32±5.05 kg/m², and 50.6% were in the normal weight, smoking and alcohol use rates were 21% and 5.3%, respectively.

Table 1: Demographic characteristics of the women (n=395)

Sociodemographic characteristics	Groups	Number	Percent
Age mean±SD 37,26±9,91	18-34	165	41.8
	35-44	138	34.9
	45-65	92	23.3
Educational status	Primary school	125	31.6
	High school	103	26.1
	University	167	42.3
Working status	Working	192	48.6
	Not working	203	51.4
Income (level)	Good	90	22.8
	Sufficient	284	71.9
	Low	21	5.3
Marital status	Married	363	91.9
	Single	32	8.1
Place of residence	Rural (district-village)	233	59.0
	Urban (province)	162	41.0
Family type	Extended family	64	16.2
	Nuclear family	331	83.8
Marriage duration (Year) mean±SD 14.13±11.14	Single	25	6.3
	1-9	128	32.4
	10-19	119	30.1
	20-29	75	19.0
	> 30	48	12.2
BMI mean±SD 25.32±5.05	Underweight	16	4.1
	Normal weight	200	50.6
	Overweight	118	29.9
	Obese	61	15.4
Active or passive smoker	Yes	83	21.0
	No	312	79.0
Drinking alcohol	Yes	21	5.3
	No	374	94.7

SD= Standard Deviation BMI=Body Mass Index

The mean HLS-EU score of women is 32.43±7.36. The mean score of the treatment and service sub-dimension is 34.04±7.32, the disease prevention sub-dimension is 32.42± 8.51, and the health promotion sub-dimension is 30.45± 9.20. It was determined that 41.5% of the women had sufficient health literacy in the treatment and service sub-dimension,

35.2% in the disease prevention sub-dimension, and 31.9% in the health promotion sub-dimension. In general, 40.3% of women have a problematic-limited level of health literacy.

Table 2 shows the relationship between participation in breast cancer screening and the health literacy levels of women in the present study. The highest rate of those who did not know BSE was among women with insufficient health literacy (20.0%). The highest rate of women who performed BSE was among women with excellent health literacy at 65.9%. In the study, a statistically significant relationship was determined between knowing what CBE is and the significance of having a female doctor in CBE and the general score of HLS-EU. (p=0.027 and p=0.019, respectively). While the rate of women who did not know what CBE was 31.7% among women with insufficient health literacy, this rate was 22.7% among women with excellent health literacy. The rate of women who stated that it was not important for them to be a female doctor in BSE was among the women with the highest health literacy of 68.2%. In the study, no statistically significant relationship was found between knowing what BSE is, performing BSE, having CBE, knowing what mammography is, having mammography and the general score of HLS-EU.

Table 3 shows the relationship between participation in cervical cancer screening and HLS-EU levels of women in this study. In the study, no statistically significant relationship was found between the HPV Vaccination Status and the HLS-EU general score. It was determined that 41.7% of the women who said no to 'knowing cervical cancer diagnosis and screening methods' had an insufficient level of health literacy and 29.5% had an excellent level of health literacy. A statistically significant relationship was determined between the level of knowing the cervical cancer diagnosis and screening methods and the general HLS-EU score (p= 0.011). It was determined that 15.1% of the women who said yes to 'the condition of having a gynecological examination' had a problematic/limited level of health literacy, and 23.3% had an insufficient level of health literacy. A statistically significant correlation was determined between the status of having a gynecological examination and the general HLS-EU score (p=0.008). While it was determined that 40.9% of the participants who stated that it is important for them to have a female gynecological examination doctor had a problematic-limited level of health literacy, this rate was 22.7% among women with an excellent level of health literacy. A statistically significant correlation was determined between that it was important for the participant herself and her husband to have a female doctor who performed a gynecological examination and the general score of HLS-EU (p=0.005 and p=0.005, respectively). While 72.7% of those who knew what the Pap smear test was, had an excellent level of health literacy, this rate was 53.3% among women with insufficient health literacy, and there was a statistically significant relationship was determined between knowing the Pap smear test and the general HLS-EU score (p=0.027). It was determined that 58.5% of the women who had a Pap smear test before had a problematic/limited level of health literacy, and 53.3% had an insufficient level of health literacy. A statistically significant relationship was determined between the status of having a Pap smear test before and the general HLS-EU score (p=0.044).

Table 2. Comparison of women's participation in breast cancer screening and the levels of HLS-EU-Q47 total and sub-dimensions

Breast cancer knowledge and early diagnostic behaviors		Insufficient		Problematic		Sufficient		Excellent		Overall		Test Statistic
		n	%	n	%	n	%	n	%	n	%	
Knowing what BSE is	Yes	38	63.3	120	75.5	89	67.4	32	72.7	279	70.6	p=0.508 x²=5.287
	Undecided	10	16.7	20	12.6	25	18.9	6	13.6	61	15.4	
	No	12	20.0	19	11.9	18	13.6	6	13.6	55	13.9	
Having BES	Yes	28	46.7	99	62.3	68	51.5	29	65.9	224	56.7	p=0.059 x²=7.431
	No	32	53.3	60	37.7	64	48.5	15	34.1	171	43.3	
Knowing what CBE is	Yes	26	43.3	105	66.0	81	61.4	31	70.5	243	61.5	p=0.027* x²=14.286
	Undecided	15	25.0	19	11.9	24	18.2	3	6.8	61	15.4	
	No	19	31.7	35	22.0	27	20.5	10	22.7	91	23.0	
Having CBE	Yes	13	21.7	57	35.8	35	26.5	10	22.7	115	29.1	p=0.093 x²=6.409
	No	47	78.3	102	64.2	97	73.5	34	77.3	280	70.9	
Knowing what mammography is	Yes	52	86.7	139	87.4	107	81.1	39	88.6	337	85.3	p=0.571 x²=4,793
	Undecided	3	5.0	11	6.9	11	8.3	1	2.3	26	6.6	
	No	5	8.3	9	5.7	14	10.6	4	9.1	32	8.1	
Having mammography	Yes	22	36.7	55	34.6	39	29.5	8	18.2	124	31.4	p=0.151 x²=5.305
	No	38	63.3	104	65.4	93	70.5	36	81.8	271	68.6	
The importance of the doctor being a woman in CBE	Yes	21	35.0	78	49.1	48	36.4	10	22.7	157	39.7	p=0.019* x²=15.159
	Undecided	4	6.7	12	7.5	17	12.9	4	9.1	37	9.4	
	No	35	58.3	69	43.4	67	50.8	30	68.2	201	50.9	

* p<0.05 ** p<0.01 BSE: Breast Self-Examination CBE: Clinical Breast Examination (CBE)

Table 3. Comparison of women's participation in cervical cancer screening and the levels of HLS-EU-Q47 total and sub-dimensions

Cervical cancer knowledge and early diagnostic behaviors		Insufficient		Problematic		Sufficient		Excellent		Overall		Test Statistic
		n	%	n	%	n	%	n	%	n	%	
Knowing cervical cancer screening methods	Yes	35	58.3	127	79.9	91	68.9	31	70.5	284	71.9	p=0.011* x²=11.088
	No	25	41.7	32	20.1	41	31.1	13	29.5	111	28.1	
Undergoing a gynecological examination	Having	46	76.7	135	84.9	100	75.8	27	61.4	308	78.0	p=0.008** x²=11.954
	Not having	14	23.3	24	15.1	32	24.2	17	38.6	87	22.0	
The importance of the doctor being a woman in the gynecological examination	Yes	13	21.7	65	40.9	37	28.0	10	22.7	125	31.6	p=0.005** x²=18.735
	Undecided	6	10.0	12	7.5	24	18.2	4	9.1	46	11.6	
	No	41	68.3	82	51.6	71	53.8	30	68.2	224	56.7	
Knowing what a Papsmear test is	Yes	32	53.3	107	67.3	74	56.1	32	72.7	245	62.0	p=0.027* x²=14.241
	Undecided	6	10.0	16	10.1	21	15.9	0	0	43	10.9	
	No	22	36.7	36	22.6	37	28.0	12	27.3	107	27.1	
Undergoing a Pap smear test	Doing	32	53.3	93	58.5	56	42.4	20	45.5	201	50.9	p=0.044* x²=8.124
	Not doing	28	46.7	66	41.5	76	57.6	24	54.5	194	49.1	
Having HPV vaccination	Having	3	5.0	9	5.7	11	8.3	2	4.5	25	6.3	p=0.699 x²=1.429
	Not having	57	95.0	150	94.3	121	91.7	42	95.5	370	93.7	

*p<0.05 **p<0.01

DISCUSSION

Three hundred ninety-five women were included in this study, which examined the effects of health literacy on breast and cervical cancer early diagnosis behaviors in women aged 18-65 living in Çorum. As the health literacy rate of women increases, health protection behaviors, including protection from diseases and early diagnosis of diseases, increase. It is possible that people with insufficient health literacy may not understand crucial health-related conditions and may not be aware of the importance of early diagnosis and screening in cancer prevention.[21,22]

In study, the mean HLS-EU Turkish version score of women was 32.43±7.36, and the health literacy level of women was problematic/limited. In the European Health Literacy Turkish Adaptation study conducted by Okyay and Abacıgil,[20] the mean score was 32.8±7.3. In studies, the mean EHLC-TR score ranges between 32.8±7.32 and 36.2±7.2.[23-26] Our findings are consistent with the findings obtained from national and international studies in the literature.

In this study the ratio of women with excellent health literacy who know the BSE are higher than those with insufficient health literacy (%72.7 and 67.4) although there is no statistically significant difference. In a study, it was determined that the health literacy level and cancer knowledge of women who participated in breast cancer screenings were better.[27]

In a study that there was a significant relationship between health literacy and breast cancer knowledge and that women with low health literacy were less likely to report their participation in monthly BSE.[12,28] In this study the highest rate of women performing BSE is 65.9% and women with excellent health literacy although here was no statistically significant difference between health literacy level and performing BSE in our study. In a study, it was determined that women with adequate health literacy were more likely to trust BSE than those with insufficient health literacy.[29] Rakhshkhorshid et al.[28] determined that women with high health literacy levels performed BSE more than others.

In this study the rate of women who do not know what CBE is higher among women with insufficient health literacy than women with excellent health literacy (31.7% and 22.7%, respectively) (**Table 2**). It has been determined that the health literacy level of women who did not undergo breast cancer screening was lower than that of women who had screening.[27] and that the increase in health literacy level increases compliance with early diagnosis behaviors.[11] It is stated that a limited level of health literacy is associated with less information-seeking behavior and this may prevent participation in screening programs.[30] This result in our study supports the view that women with a high level of health literacy have more information about breast cancer screenings and participate more in screenings.

The relationship between women's having CBE status and their health literacy level according to the EHLC-TR mean score was not statistically significant (p=0.093) (**Table 2**). The women with the lowest CBE rate are those with insufficient health literacy (21.7%). Similar to our findings, in a study conducted in Iran, no significant relationship was found between the level of health literacy and the status of CBE.[28] It is stated that individuals with a high level of health literacy may be more aware of free screening programs and this may lead the individual to have more information about screening services and benefit from non-recommended screenings.[31]

In the study, the lowest rate of those who did not know exactly what mammography was, 9.1%.was among women with excellent health literacy. In the study while the rate of not having mammography among women with limited health literacy level is 65.4%, this rate is 81.8% among women with excellent health literacy level (**Table 2**). The rate of women who have never had breast cancer screening or who have had irregular screening is 95.2% for women with insufficient health literacy and 88.2% for women with problematic

health literacy levels.[32] In a study conducted in our country, no statistically significant difference was found between the mammography status of women and the general and sub-dimension scale scores of health literacy; however, in the same study, the total and all sub-dimension scale mean scores of those who had breast cancer screening were higher. Unlike our findings, In a study it has been determined that women who had never had a mammogram before (55.2%) had a lower level of health literacy than those who had a mammogram at least once.[11] In an another studuy it has been determined that women with low and high health literacy levels had unrecommended breast cancer screening at a rate of 46.8% and 67.7%, respectively.[30] The results obtained in the studies in the literature do not show similarities with our findings. The differences in the socio-cultural characteristics of the provinces and countries where the studies were conducted may have been effective in the difference in the findings.

In study the ratio of women who has stated that it is not important for them to have a female doctor in CBE is the highest among women with excellent health literacy (68.2%) (**Table 2**). In the Muslim Turkish society, it is common for women to prefer a female physician for clinical breast examination. As a matter of fact, the barriers preventing women from participating in breast cancer screening programs are embarrassment during the examination and avoiding the examination due to religious beliefs.[33]

The ratio of women with excellent health literacy who know the cervical cancer early diagnosis and screening methods are higher than those with insufficient health literacy (70.5% and 58.3%, respectively) (p=0.011) In another study, as the level of health literacy decreases, the rate of those who have never had cervical cancer screening before or at intervals longer than 3 years increases.[32] The relationship between gynecological examination status and health literacy level according to the HLS-EU Turkish version mean score was statistically significant (p=0.008) (**Table 3**). While the rate of women with excellent health literacy level is 61.4% among women who do not have a gynecological examination, this rate is 84.9% for women with a problematic/limited level of health literacy. In a study it has been determined that women with insufficient health literacy are less likely to have a gynecological examination in the last five years compared to those with sufficient health literacy.[16] In the study of Doğan and Çetinkaya,[34] the rate of consulting to a physician for control purposes in the last 12 months is higher for people with good health literacy levels. Rutan et al.[30] determined that respectively 33.8% and 48.4% of women with low and high health literacy levels had cervical cancer screening, which is not recommended. It is stated that people with low health literacy level know less about their health, receive less preventive services, have worse physical and mental functions, and it is difficult to control chronic diseases in these individuals.[35]

The relationship between the gender of the doctor who performed the gynecological examination for screening/control purposes and the level of health literacy according to the HLS-EU Turkish version score average was statistically significant. Women with a low level of health literacy attach more importance to the gender of the doctor performing the gynecological examination. (p=0.005) (**Table 3**). While the rate of those who state that it is important for them to have a female doctor in screening/control gynecological examinations is 22.7% among women with excellent health literacy levels, this rate is 40.9% among women with problematic/limited health literacy levels. Studies on this subject are very limited. In a study conducted by Özcan et al.[36] in Gümüşhane, 86.3% of women stated that the gender of the physician who examined them was important, while 94.8% stated that they preferred a female physician.In the study of Bilgin and Doğan Merih,[37] 63.4% of women preferred a female physician for gynecological examination and 84.3% of them considered the gender of the physician when making an appointment or being examined.In the literature, that the woman does not determine the doctor who will perform the gynecological examination, privacy and the feeling of shame are shown as obstacles to the gynecological examination.[37,38] In our study, this situation may arise from that women with low health literacy levels do question their doctors' gender but rather their knowledge/experience when consulting for a gynecological examination.

The relationship between knowing what a Pap smear test is and having had a Pap smear test before and the level of health literacy according to the HLS-EU Turkish version score average was statistically significant (p=0.044) (**Table 3**). Among women with excellent health literacy levels, the rate of those who know what the Pap smear test is the highest, with 72.7%. Among women who had a previous Pap smear test, the ratio of women with excellent health literacy was higher than those with adequate health literacy (45.5% and 42.4%, respectively). While Dilli[16] determined that as the health literacy level of women increases, the level of knowledge about cervical cancer and Pap smear test increases, in another study Yılmazel[17] found that women with insufficient health literacy are less likely to have a Pap smear test than those with adequate health literacy. Thompson et al.[39] determined that there is a relationship between 'knowing that HPV is a cause in the development of cervical cancer' and having a Pap smear test in the last three years.Differently, Tiryaki and Yılmaz[14] and Şensoy[40] determined that there is no significant relationship between health literacy and Pap smear test status. Kim and Han[15] and Baharum et al.[40] state that there is a positive relationship between the level of health literacy and screening for cervical cancer. National and international findings are similar to our study results. The inadequacy of women's health literacy and health knowledge is a major obstacle to participation in cancer screenings.

In our study there was no statistically significant correlation between HPV vaccination status and health literacy level according to the HLS-EU Turkish version mean score (p=0.699). In a different study, women with insufficient health literacy were more likely to report that they had

never heard of the Pap smear test and HPV vaccine.[16] In the same study, it was stated that women with insufficient health literacy were significantly less likely to indicate that they would have a Pap smear every five years. This situation may arise because individuals with low health literacy level do not question screening procedures, or those with high health literacy level actively seek screening procedures.[30] Studies have shown that the rate of HPV vaccination among women in our country is very low.[16,41] Therefore, in our study, a significant relationship between health literacy level and HPV vaccination status may not have been determined.

CONCLUSION

In this study, it was determined that women's breast and cervical cancer information and early screening practices were insufficient and that low health literacy levels prevented women from being screened for cancer. In line with these results, it is recommended to increase awareness of breast and cervical cancer, identifying women with insufficient and limited health literacy levels, and making interventions that improve the level of health literacy through training and counseling activities which is one of the roles of nurses. In addition, planning of experimental studies examining the effects of health literacy levels on breast and cervical cancer early diagnosis behaviors are lacking. Nurses and midwives working in the field of women's health should plan initiatives to improve health literacy to increase women's participation in cancer screening.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted in accordance with the Principles of Helsinki and ethical approval was obtained from the non-interventional ethics committee of Hitit University (Date: 28.03.2019, Number: 2019-116).

Referee Evaluation Process: Externally peer-reviewed.

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Evaluation of Personal Protective Behaviors Among Healthcare Workers After Receiving COVID-19 Vaccination

COVID-19 Aşısı Yaptıran Sağlık Çalışanlarının Kişisel Koruyucu Davranışlarının Değerlendirilmesi

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Abstract

Aim: The aim of the study was to evaluate personal protective behaviors after COVID-19 vaccination in healthcare workers.

Material and Method: This cross-sectional study was conducted with healthcare workers (physician, dentist, midwife, nurse, health officer or emergency medicine technician) in Bursa City Hospital between 01.09.2021 and 01.09.2022. Data was collected with a questionnaire form which was sent to participants via an instant messaging application or email.

Results: All participants had received at least one dose of a COVID-19 vaccine and 31.0% had had experienced at least one COVID-19 infection. It was determined that while the use of N95 masks in the workplace ($p<0.001$) and in daily life ($p<0.001$) decreased following vaccination among healthcare workers, the use of three-layer surgical masks increased. The great majority did not alter behaviors after vaccination. The frequency of being present in crowded places was higher in those without a history of COVID-19 ($p=0.023$). In the multivariable regression analysis, a reported 'decrease' in the number of masks used in the workplace was associated with profession (those other than Nurse/Midwife/Health officer) and smoking status (non-smokers) ($p=0.001$ and $p=0.025$, respectively).

Conclusions: It can be said that healthcare professionals maintain their personal protective behaviors in the hospital and in daily life even after receiving COVID-19 vaccination. Of note, healthcare workers other than Nurse/Midwife/Health officer and non-smokers had a higher likelihood of reporting a decrease in the number of masks they were using in the workplace.

Keywords: Pandemic, SARS-CoV-2, COVID-19 vaccines, personal protective equipment

Öz

Amaç: Çalışmanın amacı, sağlık çalışanlarında COVID-19 aşılaması sonrası kişisel koruyucu kullanım davranışların değerlendirilmesidir.

Gereç ve Yöntem: Bu kesitsel araştırma, 01.09.2021-01.09.2022 tarihleri arasında Bursa Şehir Hastanesinde sağlık çalışanları (hekim, diş hekimi, ebe, hemşire, sağlık memuru veya acil tıp teknisyeni) ile yapılmıştır. Veriler anket formu ile toplanmış ve bir anlık mesajlaşma uygulaması veya e-posta yoluyla katılımcılara gönderilmiştir.

Bulgular: Tüm katılımcılar en az bir doz COVID-19 aşısı almıştı ve %31.0'ı en az bir COVID-19 enfeksiyonu geçirmişti. Sağlık çalışanlarında aşılama sonrası işyerinde ($p<0.001$) ve günlük hayatta ($p<0.001$) N95 maske kullanımı azalırken, üç katlı cerrahi maske kullanımının arttığı belirlendi. Büyük çoğunluk aşılamadan sonra davranışlarını değiştirmedi. COVID-19 öyküsü olmayanlarda kalabalık ortamlarda bulunma sıklığı daha yüksekti ($p=0.023$). Çok değişkenli regresyon analizinde işyerinde kullanılan maske sayısında bildirilen 'azalma' meslek (Hemşire/Ebe/Sağlık memuru dışındakiler) ve sigara içme durumu (sigara içmeyenler) ile ilişkilendirildi ($p=0.001$ ve $p=$ sırasıyla 0.025).

Sonuç: Sağlık profesyonellerinin hastanede ve günlük yaşamda kişisel koruyucu davranışlarını COVID-19 aşısı olduktan sonra bile sürdürdükleri söylenebilir. Hemşire/Ebe/Sağlık memuru ve sigara içmeyenler dışındaki sağlık çalışanlarının işyerinde kullandıkları maske sayısında azalma bildirme olasılıklarının daha yüksek olduğunu belirtmek gerekir.

Anahtar Kelimeler: Pandemi, SARS-CoV-2, COVID-19 aşıları, kişisel koruyucu ekipman

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INTRODUCTION

The cause of COVID-19, declared a pandemic by the World Health Organization (WHO) on 11.03.2022, is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The global crisis caused by COVID-19 can still be considered one of the largest public health crises, well into its third year.[2,3] As of 12.10.2022, there are 605,912,418 confirmed cases of COVID-19, including 6,491,649 deaths reported worldwide. In Türkiye, there are 16,829,941 confirmed cases, with 100,979 deaths.[4]

COVID-19 pandemic has prompted scientists and public health officials around the world to rapidly improve our knowledge of this disease and develop new measures. Vaccines are the most effective long-term strategy to control and prevent the COVID-19 pandemic.[2] According to WHO data, 12,589,972,108 doses of COVID-19 vaccine were administered worldwide and a total of 152,059,687 doses were administered in Türkiye (as of September 2022).[4] Alongside vaccines, multi-layered interventions, which also include preventive measures to reduce the spread of COVID-19, are important in pandemic control.[2,5] Since the beginning of the pandemic, those who perceive SARS-CoV-2 as a threat have implemented preventive measures against the disease, such as frequent testing, contact tracing, vaccination programs and personal protective measures (hand cleaning, physical distancing, wearing masks, etc.).[6]

"Peltzman Effect" is about individuals' respond to safety measures with a compensatory increase in risky behavior.[7-9] There is not enough evidence yet on the behavioral responses of society to preventive measures after COVID-19 vaccination. While a high vaccination rate is critical to end the pandemic, increased vigilance in infectious cases and reduced preventive measures due to a heightened sense of perceived security could lead to an alarming increase in cases.[10] The aim of the study was to evaluate the PPB of healthcare workers after receiving COVID-19 vaccine(s).

MATERIAL AND METHOD

This cross-sectional study was carried out with healthcare professionals at Bursa City Hospital between 01.09.2021 and 01.09.2022. Ethics committee approval was obtained from Bursa City Hospital Ethics Committee (Date: 22.09.2021, Decision No: 2021-17/5).

Healthcare professionals (physicians, dentists, midwives, nurses, health officers or emergency medicine technicians) were included in the study group. The questionnaire form was distributed through an instant messaging application and e-mail groups and applied between 7.10.2021 and 31.11.2021 via Google forms. In the questionnaire, sociodemographic characteristics, employment status, medical history, COVID-19 vaccination history and personal protective equipment (PPE) usage were asked. Smoking status, chronic diseases, isolation measures, and type of masks used (none, cloth mask, surgical masks, respirators –referred to as N95) were also gathered. According to the Centers for Disease Control and Prevention (CDC), the N95 mask is the type of mask that filters at least 95% of airborne particles.[11] Participants were asked about their PPB (handwashing frequency, daily mask count, disinfectant usage, exposure to crowds) and their usage of PPE before and after vaccination. To make comparisons, they were expected to provide a relative response regarding their post-vaccination behaviors compared to their pre-vaccination behaviors (decreased, same, increased). Perception of safety following vaccination was scored on a Likert scale, '0' indicated that they did not feel safe at all, while '5' indicated absolute certainty of safety. In the preparation of the questions, COVID-19 guide prepared by the Ministry of Health of the Republic of Türkiye was used.[12]

The COVID-19 vaccine used for the first time in Türkiye was administered to healthcare personnel and then population aged 65 and over.[13] According to the most recently updated data (25.09.2022), 93.32% of the population had received at least a single dose of either vaccine, while completed (two doses) vaccination was reported as 85.64%.[14]

Statistical Analysis

All analyses were performed using IBM SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). For the normality check, the Kolmogorov-Smirnov test was used. Data are given as median (1st quartile-3rd quartile) for continuous variables according to non-normality of distribution, and as frequency (percentage) for categorical variables. Mask type before and after vaccination were analyzed with the marginal homogeneity test. Between groups analyses were performed with the chi-square test. Logistic regression analyses were performed to determine significant factors independently associated with the decrease in mask usage frequency at work. Variables were analyzed with univariate regression analysis and those with statistical significance were included into the multivariate model. The statistical significance threshold was accepted as $p < 0.05$.

RESULTS

Among participants, 81.8% were female and 18.2% were male, median age was 35 (22-62). The frequency of experiencing COVID-19 at least once was 31.0% and the frequency of direct contact with COVID-19 cases was 83.0%. The entire research group had received at least one dose of vaccine. The frequency of four doses of vaccine in the study group was 21.9%. The frequency of healthcare professionals feeling "safe" after vaccination was 91.4% (**Table 1**).

Table 1. Summary of participants' characteristics and vaccination status

Age, years, (range 22-62)	35 (27-43)
Sex	
Female	477 (81.8%)
Male	106 (18.2%)
Marital status	
Married	388 (66.6%)
Single	195 (33.4%)
Occupation	
Physician	83 (14.2%)
Nurse/Midwife/Health officer	421 (72.2%)
Other medical personnel	79 (13.6%)
Duration of employment, years (range: 0.75-39)	12 (3-20)
Smoking status	
Non-smoker	344 (59.0%)
Ex-smoker	65 (11.1%)
Smoker	174 (29.8%)
Chronic disease	149 (25.6%)
Diabetes mellitus	19 (3.3%)
Hypertension	38 (6.5%)
COPD	3 (0.5%)
Asthma	34 (5.8%)
Heart diseases	17 (2.9%)
Malignancy	8 (1.4%)
Other	82 (14.1%)
COVID-19 infection history	
None	402 (69.0%)
One time	174 (29.8%)
Two times	7 (1.2%)
Isolation due to contact	134 (23.0%)
Direct contact with patients	484 (83.0%)
Doses of COVID-19 vaccination	
1	15 (2.6%)
2	145 (24.9%)
3	295 (50.6%)
4	128 (21.9%)
COVID-19 vaccination (1st dose)	
No	0 (0.0%)
Biontech	59 (10.1%)
Sinovac	524 (89.9%)
COVID-19 vaccination (2nd dose)	
No	15 (2.6%)
Biontech	58 (9.9%)
Sinovac	510 (87.5%)
COVID-19 vaccination (3rd dose)	
No	160 (27.4%)
Biontech	367 (63.0%)
Sinovac	56 (9.6%)
COVID-19 vaccination (4th dose)	
No	455 (78.0%)
Biontech	122 (20.9%)
Sinovac	6 (1.0%)
Type of vaccine received	
Only Biontech	55 (9.4%)
Only Sinovac	154 (26.4%)
Both	374 (64.2%)
Feeling "safe" after vaccination	
0 (Not at all)	50 (8.6%)
1	34 (5.8%)
2	93 (16.0%)
3	201 (34.5%)
4	139 (23.8%)
5 (Absolutely)	66 (11.3%)

Data are given as median (1st quartile-3rd quartile) for continuous variables according to non-normality of distribution and as frequency (percentage) for categorical variables
COPD: Chronic obstructive pulmonary disease

It was determined that three people before the vaccination and two people after the vaccination did not use masks. Cloth mask usage frequency before vaccination was 6.0%, while it was 6.9% after vaccination. It was determined that while the use of N95 masks decreased in the workplace ($p<0.001$) and daily life ($p<0.001$) after vaccination, the use of three-layer surgical masks increased (**Table 2**).

Table 2. Type of mask before and after vaccination

	Before vaccination	After vaccination	p
At work			
None	3 (0.5%)	2 (0.3%)	<0.001
Cloth mask	35 (6.0%)	40 (6.9%)	
Surgical mask	374 (64.2%)	415 (71.2%)	
Respirators (N95, etc.)	171 (29.3%)	126 (21.6%)	
Daily life			
None	7 (1.2%)	9 (1.5%)	<0.001
Cloth mask	45 (7.7%)	49 (8.4%)	
Surgical mask	460 (78.9%)	483 (82.8%)	
Respirators (N95, etc.)	71 (12.2%)	42 (7.2%)	

Data are given as frequency (percentage)

After vaccination, the vast majority of healthcare workers continued their behavior of washing hands at work, washing hands in daily life, using masks at work, using masks in daily life, using disinfectants at work, and using disinfectants in daily life. Most importantly, only a marginal proportion of participants reported a decrease in these protective measures after vaccination (**Table 3**).

Table 3. Change in protective behaviors after vaccination

Handwashing frequency at work	
Decreased	18 (3.1%)
Same	461 (79.1%)
Increased	104 (17.8%)
Handwashing frequency in daily life	
Decreased	20 (3.4%)
Same	461 (79.1%)
Increased	102 (17.5%)
Number of masks used in work	
Decreased	47 (8.1%)
Same	428 (73.4%)
Increased	108 (18.5%)
Number of masks used in daily life	
Decreased	45 (7.7%)
Same	441 (75.6%)
Increased	97 (16.6%)
Disinfectant usage frequency at work	
Decreased	62 (10.6%)
Same	419 (71.9%)
Increased	102 (17.5%)
Disinfectant usage frequency in daily life	
Decreased	72 (12.3%)
Same	416 (71.4%)
Increased	95 (16.3%)
Frequency of being present in crowded places	
Decreased	69 (11.8%)
Same	365 (62.6%)
Increased	149 (25.6%)

Data are given as frequency (percentage)

There was no relationship between feeling safe after vaccination and having a chronic disease (p=0.940). The distribution of mask types used in the workplace (p=0.818) and in daily life (p=0.753) after vaccination was similar between those with and without chronic disease. There was no relationship between having a chronic disease and handwashing frequency at work (p=0.969), handwashing frequency in daily life (p=0.890), number of masks used at work (p=0.691), number of masks used in daily life (p=0.842), disinfectant usage frequency at work (p=0.792), disinfectant usage frequency in daily life (p=0.906) (**Table 4**).

Table 4. Summary of protective behaviors after vaccination with regard to chronic disease

	Chronic disease		
	Absent (n=434)	Present (n=149)	p
Feeling "safe" after vaccination			
0 (Not at all)	37 (8.5%)	13 (8.7%)	0.940
1	27 (6.2%)	7 (4.7%)	
2	67 (15.4%)	26 (17.4%)	
3	152 (35.0%)	49 (32.9%)	
4	104 (24.0%)	35 (23.5%)	
5 (Absolutely)	47 (10.8%)	19 (12.8%)	
Type of mask, at work			
None	1 (0.2%)	1 (0.7%)	0.818
Cloth mask	31 (7.1%)	9 (6.0%)	
Surgical mask	307 (70.7%)	108 (72.5%)	
Respirators (N95, etc.)	95 (21.9%)	31 (20.8%)	
Type of mask, daily life			
None	6 (1.4%)	3 (2.0%)	0.753
Cloth mask	38 (8.8%)	11 (7.4%)	
Surgical mask	361 (83.2%)	122 (81.9%)	
Respirators (N95, etc.)	29 (6.7%)	13 (8.7%)	
Handwashing frequency at work			
Decreased	13 (3.0%)	5 (3.4%)	0.969
Same	343 (79.0%)	118 (79.2%)	
Increased	78 (18.0%)	26 (17.4%)	
Handwashing frequency in daily life			
Decreased	15 (3.5%)	5 (3.4%)	0.890
Same	345 (79.5%)	116 (77.9%)	
Increased	74 (17.1%)	28 (18.8%)	
Number of masks used in work			
Decreased	37 (8.5%)	10 (6.7%)	0.691
Same	315 (72.6%)	113 (75.8%)	
Increased	82 (18.9%)	26 (17.4%)	
Number of masks used in daily life			
Decreased	35 (8.1%)	10 (6.7%)	0.842
Same	328 (75.6%)	113 (75.8%)	
Increased	71 (16.4%)	26 (17.4%)	
Disinfectant usage frequency at work			
Decreased	44 (10.1%)	18 (12.1%)	0.792
Same	313 (72.1%)	106 (71.1%)	
Increased	77 (17.7%)	25 (16.8%)	
Disinfectant usage frequency in daily life			
Decreased	54 (12.4%)	18 (12.1%)	0.906
Same	311 (71.7%)	105 (70.5%)	
Increased	69 (15.9%)	26 (17.4%)	
Frequency of being present in crowded places			
Decreased	51 (11.8%)	18 (12.1%)	0.297
Same	265 (61.1%)	100 (67.1%)	
Increased	118 (27.2%)	31 (20.8%)	

Data are given as median (1st quartile-3rd quartile) for continuous variables according to non-normality of distribution and as frequency (percentage) for categorical variables

No correlation was found between safety perception after vaccination and history of COVID-19 (p=0.142). The distribution of mask types used in the workplace (p=0.352) and in the daily life environment (p=0.407) after vaccination was similar between those with and without a history of COVID-19. There was no relationship between having a history of COVID-19 and handwashing frequency at work (p=0.939), handwashing frequency in daily life (p=0.554), number of masks used at work (p=0.087), number of masks used in daily life (p=0.155), disinfectant usage frequency at work (p=0.189) and disinfectant usage frequency in daily life (p=0.213)(**Table 5**).

Table 5. Summary of protective behaviors after vaccination with regard to COVID-19 disease history

	COVID-19 disease history		
	Absent (n=402)	Present (n=181)	p
Feel safe after vaccination			
0 (None)	32 (8.0%)	18 (9.9%)	0.142
1	18 (4.5%)	16 (8.8%)	
2	67 (16.7%)	26 (14.4%)	
3	134 (33.3%)	67 (37.0%)	
4	100 (24.9%)	39 (21.5%)	
5 (Absolutely)	51 (12.7%)	15 (8.3%)	
Type of mask, at work			
None	2 (0.5%)	0 (0.0%)	0.352
Cloth mask	29 (7.2%)	11 (6.1%)	
Surgical mask	278 (69.2%)	137 (75.7%)	
Respirators (N95, etc.)	93 (23.1%)	33 (18.2%)	
Type of mask, daily life			
None	8 (2.0%)	1 (0.6%)	0.407
Cloth mask	37 (9.2%)	12 (6.6%)	
Surgical mask	328 (81.6%)	155 (85.6%)	
Respirators (N95, etc.)	29 (7.2%)	13 (7.2%)	
Handwashing frequency at work			
Decreased	12 (3.0%)	6 (3.3%)	0.939
Same	317 (78.9%)	144 (79.6%)	
Increased	73 (18.2%)	31 (17.1%)	
Handwashing frequency in daily life			
Decreased	16 (4.0%)	4 (2.2%)	0.554
Same	316 (78.6%)	145 (80.1%)	
Increased	70 (17.4%)	32 (17.7%)	
Number of masks used in work			
Decreased	39 (9.7%)	8 (4.4%)	0.087
Same	288 (71.6%)	140 (77.3%)	
Increased	75 (18.7%)	33 (18.2%)	
Number of masks used in daily life			
Decreased	36 (9.0%)	9 (5.0%)	0.155
Same	296 (73.6%)	145 (80.1%)	
Increased	70 (17.4%)	27 (14.9%)	
Disinfectant usage frequency at work			
Decreased	49 (12.2%)	13 (7.2%)	0.189
Same	283 (70.4%)	136 (75.1%)	
Increased	70 (17.4%)	32 (17.7%)	
Disinfectant usage frequency in daily life			
Decreased	56 (13.9%)	16 (8.8%)	0.213
Same	283 (70.4%)	133 (73.5%)	
Increased	63 (15.7%)	32 (17.7%)	
Being in crowded places frequency			
Decreased	44 (10.9%)	25 (13.8%)	0.023
Same	242 (60.2%)	123 (68.0%)	
Increased	116 (28.9%)	33 (18.2%)	

Data are given as median (1st quartile-3rd quartile) for continuous variables according to non-normality of distribution and as frequency (percentage) for categorical variables

Multivariate logistic regression analysis revealed that occupation and smoking status were independently associated with reporting a "decrease" in the number of masks used in the workplace after vaccination. Nurse/midwife/health officers (p=0.001) were less likely to report a decrease in the number of masks used in the workplace after vaccination than physicians and other medical personnel; whereas, non-smokers (p=0.025) were more likely to report a decrease in the number of masks used in the workplace after vaccination than ex-smokers and smokers (**Table 6**, **Figure 1**, **Figure 2**).

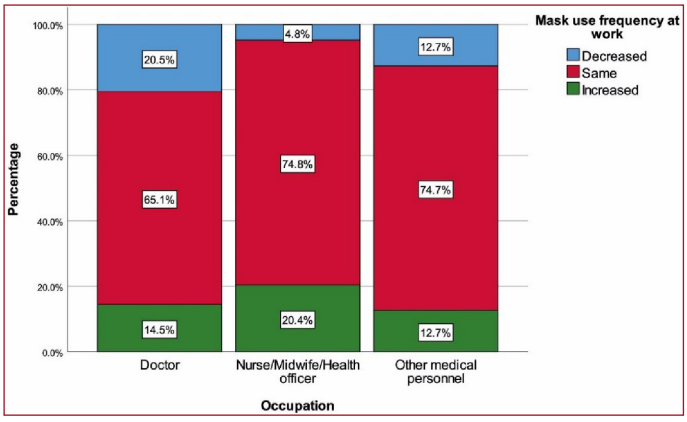

Figure 1. Change in mask use frequency at work after vaccination with regard to occupation

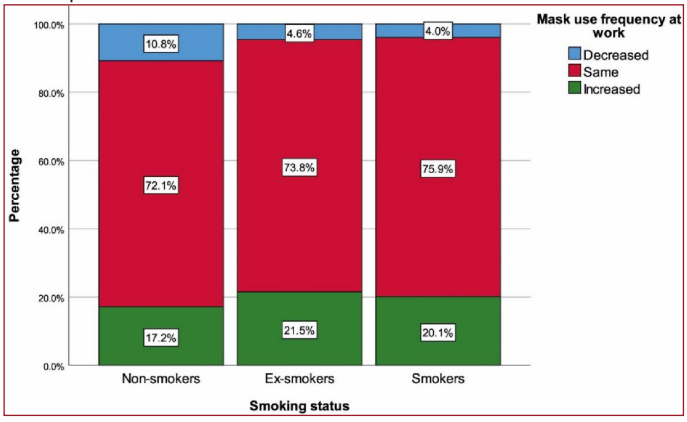

Figure 2. Change in mask use frequency at work after vaccination with regard to smoking status

DISCUSSION

The impact of vaccination in controlling the spread of SARS-CoV-2 varies widely, depending not only on efficacy and coverage, but also on concurrent adherence to non-pharmaceutical interventions.[15] The decrease in personal protective measures in the society may cause an uncontrolled increase in cases.[10] It becomes even more important that individuals do not pay attention to measures, as it may coincide with the rise of variants.[16]

The value of face masks is further increased by the ongoing uncertainty of the pandemic, the emergence of new variants, reduced vaccine efficacy, diminished immunity, seasonal variation in case numbers and increased contagion. COVID-19 peaks have raised questions about whether or how long face masks will be required.[5] Vaccination protects from disease development, nonetheless immunity decreases a few months after vaccination. Masks, on the other hand, play an important role in the control of infection by interfering with transmission, regardless of antibody level and variant.[3] Healthcare professionals, caregivers and visitors should wear an appropriate mask when caring for patients with or without COVID-19, maintaining hand hygiene each time they touch their medical mask or face, and continuing to adhere to physical distancing.[17] Vaccinated individuals may have a false perception of their long-term immunity. This may have negative consequences, such as delaying booster doses or decreasing compliance with PPB.[18]

In a study conducted, it was reported that mask usage frequency reduced by 22% after vaccination.[19] In the study by Varas et al., unvaccinated participants were found to be less likely to stop physical distancing than participants who received at least one dose of vaccine. On the other hand, it has been reported that vaccination is not one of the predictive factors of mask use and hand washing.[20] Karayürek et al. reported that the vaccine had a positive effect on reducing the fear and anxiety levels of dentists, but adherence to protective measures reduced after vaccination (such as the use of PPE and pre-operative

Table 6. Factors associated with decrease the number of masks used in work after vaccination, logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age, years	0.981 (0.948-1.017)	0.297		
Sex, Male	0.772 (0.336-1.775)	0.543		
Marital status, Single	0.661 (0.335-1.305)	0.233		
Occupation, Nurse/Midwife/Health officer	0.249 (0.135-0.459)	<0.001	0.328 (0.169-0.635)	0.001
Duration of work, years	0.979 (0.947-1.012)	0.205		
Smoking status, Non-smoker	2.760 (1.344-5.666)	0.006	2.342 (1.114-4.922)	0.025
Chronic disease	0.772 (0.374-1.593)	0.484		
COVID-19 disease history	0.430 (0.197-0.941)	0.035	0.455 (0.203-1.022)	0.057
Isolation due to contact	1.163 (0.586-2.310)	0.665		
Direct contact with patients	1.435 (0.592-3.477)	0.424		
Doses of COVID-19 vaccination, 4 doses	1.954 (1.032-3.699)	0.040	0.901 (0.438-1.856)	0.778
Type of vaccination, Only Sinovac	0.384 (0.160-0.923)	0.032	0.445 (0.177-1.121)	0.086
Type of mask at work before vaccination, Respirators	2.078 (1.135-3.807)	0.018	1.563 (0.825-2.963)	0.171
Nagelkerke R2	-		0.136	

OR: Odds Ratio, CI: Confidence Interval

mouth rinsing).[21] There are also studies reporting positive changes in PPB after vaccination. For instance, Calamari et al. reported that vaccinated people had higher mask usage than unvaccinated people.[22] In a study conducted by Zhang et al. with healthcare professionals, PPB demonstrated a significant positive change after vaccination.[23] In another study conducted among healthcare professionals, it was reported that the correct mask usage rates increased significantly after vaccination.[24] In the current study, it was determined that PPB such as the number of masks used by healthcare professionals, hand hygiene and social distancing remained at the same levels after vaccination. Of note, there was no relationship between daily mask counts and vaccination status in multivariable analysis. Previously, healthcare professionals were not found to decrease their PPB even when they experienced a positive perception of safety following vaccination,[25] similar to our results. Kaim et al. reported that social distancing and mask use were not associated with vaccination.[26] Similar results have been demonstrated in different studies, which demonstrates that healthcare professionals' PPB have not changed after vaccination.[27,28] The fact that the current research group consists of healthcare personnel, the high level of compliance with PPB or the support provided by health policies and trainings for PPB may be among the reasons causing this strict adherence to measures. Differences in COVID-19 control techniques, policies and socioeconomic levels between countries at the time of studies could influence adherence to protective measures and personal perceptions associated with vaccination.

The effectiveness of face masks on the incidence of COVID-19 is dependent on mask material and mask fit.[3] WHO states that filtering and breathability are important characteristics of masks, and that cloth (fabric) masks should be constructed with three layers. The innermost layer of cloth masks should consist of absorbent material such as cotton, the middle layer of non-absorbent material such as polypropylene and the outermost layer of non-absorbent material such as polyester or polyester blend.[17] The frequency of cloth mask usage among healthcare professionals in our study group was 6% before vaccination and 6.9% after vaccination. It was concluded that the use of cloth masks, which are likely to be unsafe due to the lower frequency of replacement and the variety of materials produced, is a subject that should be investigated more.

Being a healthcare professional during the COVID-19 pandemic is an independent predictor of higher mask usage frequency.[22] In another study, it was reported that the change in the correct mask usage rates of physicians and nurses after the COVID-19 vaccine was found to be similar.[24] Lopez et al. reported that there was no difference between professions in terms of social distancing and PPB.[25] In another study, it was reported that nurses and physicians were similar in terms of appropriate use of PPE for COVID-19.[27] In the current study, nurse/midwife/health officer professions were less likely to decrease the number of masks they used in the hospital than physicians and other health personnel. Similarly, in the study of Zhang et al. it was reported that healthcare professionals with higher education levels had better knowledge about COVID-19, but had worse PPB.[23] Since the number of masks used in a day varies in terms of the number of situations that a healthcare personnel touches or needs to change their mask and the mobility of the department where they work, the decreasing number of masks in some healthcare personnel may not necessarily indicate inappropriate mask use. While those in the nurse/midwife/health officer profession did not reduce the number of masks they use for their job, physicians may have experienced a change in workload. Since our data are based on self-reports of healthcare professionals due to cross-sectional design, we cannot directly evaluate the appropriateness of masks use among healthcare personnel.

Since smoking behavior is characterized by inhalation and repetitive hand-mouth movements that are recommended to be avoided to reduce viral contamination, it is expected that smokers will not comply with personal protective measures necessary to prevent COVID-19 spread.[29] Peixoto et al. reported that ex-smokers are more likely to wear masks in public than current and non-smokers.[30] Other previously published studies have reported that individuals who do not smoke or smoke less are more likely to comply with COVID-19 preventive measures.[31-34] On the other hand, Massey et al. reported that risk communication about COVID-19 and smoking was associated with higher mask wearing among smokers.[35] In this study, the number of masks used by non-smokers at work was found to be more likely to decrease. This may have been because smokers and ex-smokers may have remained concerned about possible exposure due to their perception of being in a high-risk group.

Patterson et al. reported that those who perceive COVID-19 as a serious risk tended to have personal health concerns and were taking protective measures.[36] It is reported that chronic disease status is significantly associated with COVID risk perceptions and the desire to be vaccinated.[37] Chan et al. reported that there was no relationship between having a chronic disease and preventive measures against COVID-19.[38] In two previous studies, no relationship was found between compliance with social distancing and the presence of comorbidity.[32,39] In this study, similar to the studies in the literature, no significant difference was found between those with and without chronic diseases in terms of personal protective measures after vaccination.

Previous history of COVID-19 has been directly associated with decreased adherence to both social distancing and personal protective measures.[25] Kaim et al. reported that those infected with the COVID-19 were less likely to wear masks or adhere to social distancing compared to vaccinated individuals without a history of COVID-19.[26] In a prospective study by Calamari et al., previous COVID-19 was initially found

to be unrelated to mask usage; however, follow-up analysis revealed that COVID-19 history was one of the independent factors associated with reduced mask usage.[22] In the present study, no relationship was found between COVID-19 history and various factors, including safety perception after vaccination, the distribution of mask types used and the frequency of protective behavior; however, the frequency of being in crowded places was found to be higher in those who did not have a history of COVID-19. Differences between the time elapsed since the infection, the severity of the previous infection and the case/vaccination rates in the population where the studies were conducted may have affected the results.

Enforcing and supporting vaccinations whenever possible and ensuring sustainability of personal protective measures remain as the best approaches against the ongoing pandemic.[6] Recommending continuation of protective behaviors after vaccination is unlikely to be effective when the number of cases in the population is very low. Establishing a clearly articulated, realistic, understandable, reliable and actionable set of priorities that sets out the best practices to follow after vaccination can be beneficial to the continuity of public health protection.[16]

The cross-sectional design of this study is one of the most important limitations which prevents time-bound analyses that could have provided more reliable information regarding causality. In relation, we asked individuals to characterize their frequency of protective measures in three groups (increased, decreased, same), which may be a problematic approach since this only assesses quantity without discerning the qualitative aspect of individual measures. Direct observation of appropriateness of behaviors would have provided stronger evidence. The fact that the study was conducted in a single center with very high vaccine adherence is another limitation. Despite these, the results of this research are valuable as they share detailed results regarding the relationships between vaccination and PPB of healthcare professionals.

CONCLUSIONS

As a result, it can be concluded that there is no remarkable loss of focus regarding PPB after COVID-19 vaccination among healthcare professionals. Non-smokers and healthcare professionals other than nurses, midwives and health officers were more likely to decrease the number of masks they used in the workplace. There was no relationship between the presence of chronic disease and PPB. No relationship was found between PPB and a history of COVID-19, except that those without a history of COVID-19 were more likely to be present in crowded places. There is a need for population-based and prospective studies evaluating vaccination and PPB in the population, with a potential view to assess the influence of healthcare professionals' attitudes on this matter.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from Bursa City Hospital Ethics Committee (Date: 22.09.2021, Decision No: 2021-17/5).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Orijinal Araştırma

Outcomes of Meningioma Patients Undergoing Stereotactic Radiotherapy

Stereotaktik Radyoterapi Uygulanan Menengiom Tanılı Olgularda Tedavi Sonuçlarımız

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Abstract

Aim: Innovations in radiotherapy have paved the way for alternative approaches for the treatment of meningioma, and in this context, radiosurgery has begun to be used in the treatment of meningioma. This study aimed to examine the clinical results of radiosurgery in the treatment of meningioma and to show whether it achieves the main goals, especially in terms of the possibility of tumor control and the success of preventing progression.

Material and Method: Primary, residual, and recurrent meningioma treated with stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) between 2013 and 2020 were evaluated retrospectively. Study endpoints were overall survival (OS), progression free survival (PFS), and local control (LC).

Results: 73 patients and 81 lesions were analyzed. The median duration of the follow-up period was 49 months (range, 7–138 months). 5- and 7-y OS and PFS were 87.6%, 78.9%; 82.9% and 82.9%, respectively. The tumor control rate was 94.6%. In univariate analysis, gender (p=0.007), radiosurgery for recurrence (p=0.011) and number of lesions (p=0.030) were found to be factors affecting OS, and number of lesions (p<0.001), grade (p=0.048) and tumor size (p=0.047) were found to be factors affecting PFS. Number of lesions (p=0.022) was remained prognostic factor for PFS in the multivariate analysis.

Conclusion: Since SRS/SRT can provide high tumor control in the management of meningioma, it can be preferred as an alternative treatment method, especially in patients who are diagnosed radiologically, who are not candidates for surgery or who refuse surgical treatment, as well as in cases of residual and recurrence in the post-surgical period.

Keywords: Meningioma, stereotactic radiosurgery, stereotactic radiotherapy

Öz

Amaç: Radyoterapideki yenilikler menengiom tedavisinde alternatif yaklaşımların önünü açmış ve bu bağlamda radyocerrahi menengiom tedavisinde kullanılmaya başlanmıştır. Bu çalışma, radyocerrahinin menengiom tedavisinde klinik sonuçlarını incelemek ve özellikle tümör kontrolü olasılığı ve ilerlemeyi önleme başarısı açısından ana hedeflere ulaşıp ulaşmadığını göstermeyi amaçladı.

Gereç ve Yöntem: 2013-2020 yılları arasında stereotaktik radyocerrahi (SRC) ve stereotaktik radyoterapi (SRT) ile tedavi edilen primer, rezidüel ve nüks menengiomlar retrospektif olarak değerlendirildi. Çalışma son noktaları, genel sağkalım (GS), progresyonsuz sağkalım (PS) ve lokal kontrol (LK) idi.

Bulgular: 73 hasta ve 81 lezyon analiz edildi. Medyan takip süresi 49 aydı (aralık, 7-138 ay). 5- ve 7-y GS ve PS sırasıyla %87,6, %78,9; ve %82,9, %82,9'du. Tümör kontrol oranı %94,6'ydı. Tek değişkenli analizde cinsiyet (p=0,007), nüks nedeniyle radyocerrahi (p=0,011) ve lezyon sayısı (p=0,030) GS'ı etkileyen faktörler olarak bulundu ve lezyon sayısı (p<0,001), grad (p= 0,048) ve tümör boyutu (p=0,047) PS'ı etkileyen faktörler olarak bulundu. Çok değişkenli analizde lezyon sayısı (p=0,022) PS için prognostik faktör olarak kaldı.

Sonuç: SRC/SRT menengiom tedavisinde yüksek tümör kontrolü sağlayabildiği için özellikle radyolojik olarak tanı konulan, cerrahiye aday olmayan veya cerrahi tedaviyi reddeden hastalarda, aynı zamanda ameliyat sonrası dönemde rezidüel ve nüks durumlarında alternatif bir tedavi yöntemi olarak tercih edilebilir.

Anahtar Kelimeler: Menengiom, stereotaktik radyocerrahi, stereotaktik radyoterapi

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INTRODUCTION

Today, the prevalence of meningioma diagnosis has increased with the prolongation of life expectancy and the more frequent and easier access to imaging techniques. [1] Since they have a slow growth pattern, they are usually asymptomatic unless they are adjacent to the critical structure and are detected incidentally without any neurological findings. The presence of symptoms, the location and size of the tumor, as well as the patient's preference are the factors that should be considered in the management of meningioma.[2,3] While incidentally detected, asymptomatic, small lesions can be followed, radical surgery is often preferred for large lesions or for symptomatic relief in cases with neurological findings. [3] However, surgery is not appropriate in eloquent areas due to the increased risk of cranial nerve deficit or vascular damage. Radiosurgery can be applied as an alternative to surgery in patients for whom surgery is not suitable or depending on the patient's request.

The innovations in radiotherapy opened alternative approaches for the treatment of meningioma. Radiosurgery has been used in the treatment of meningioma for about 30 years.[4] There is no randomized study comparing surgery and radiosurgery yet, but results from radiosurgery studies including large series confirm that radiosurgery can be an alternative to surgery. In a retrospective study comparing radical surgery and radiosurgery in small meningiomas, local control was shown to be similar.[5] Radiosurgery in benign meningiomas has been shown to provide local control (LC) rates ranging from 85-97% in 5 years in many large series.[6-8] In addition, adjuvant radiosurgery following subtotal excision of benign meningiomas has yielded satisfactory results.[9] Radiosurgery is often added to surgery as a combined treatment in skull base meningiomas where gross total excision is not possible.[10] Finally, radiosurgery is applied in recurrent disease.[3]

Currently, radiosurgery is applied in the treatment of meningioma with the indications mentioned above, so in this study, we aimed to examine the clinical outcomes of radiosurgery in the treatment of meningioma and to show whether it achieves the main goals, particularly in terms of the possibility of tumor control and the success of preventing progression.

MATERIAL AND METHOD

Patient Selection and Data Collection

For this single-center retrospective analysis, all consecutive cases of primary, residual, and recurrent intracranial meningioma treated with stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) between October 2013 and December 2020 were evaluated. Patients with a histologically or radiologically confirmed diagnosis and patients older than 18 years of age were included. Patients who received more than 5 fractions were excluded from the study. Patient charts were reviewed and demographic information of patients, tumor and treatment characteristics, clinical outcomes and treatment-induced adverse events are all reported. The study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethics committee of our institute. Individual approval was waived due to retrospective design. The study was approved by The University of Health Sciences, Samsun Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (No:2021/12/3, Date:23.6.2021)

Treatment Planning

CyberKnife® (Accuray, Sunnyvale, USA) Robotic Radiosurgery System was used in radiosurgery technique. For treatment planning, the software Multiplan v4.5 and 6D Skull Tracking system were used for treatment planning and delivery. Simulation computed tomography was performed with a slice thickness of 1 mm. A custom-made aquaplast mask was used for immobilization. Target structures were contoured after image fusion with T1-weighted magnetic resonance image with gadolinium contrast. The gross tumor volume (GTV) was defined as contrast-enhanced mass. The planning target volume was obtained by adding 1 mm to the GTV in 7 patients, otherwise it was the same as the GTV. Treatment was administered in single or multiple fractions depending on target volume and proximity to critical structures.

Follow-up

The patients were followed up regularly both clinically and radiologically. All patients were seen 1-3 months after treatment to assess the presence of symptoms associated with acute toxicity. Symptom control was recorded as clinical improvement or stability and no new complaints after SRS/SRT. Serial radiological evaluations were performed at 6-month intervals in all patients after the first imaging was performed 3 or 6 months after treatment.

Tumor responses were evaluated radiologically during the follow-up period. Local failure was defined as tumor growth greater than 2 mm in at least one of the tumor diameters. Distant failure was defined as a new lesion outside the initial treatment region. LC was defined as a stable response and/or partial response with tumor shrinkage.

Endpoints and Statistical Analysis

Study endpoints were overall survival (OS), progression free survival (PFS), and LC. OS was defined as the time elapsed between the date of treatment to the date of death or lost to follow-up. PFS was calculated as the time elapsed between the date of treatment to the date of radiographic evidence of a new lesion outside the SRT field or the date of radiographic evidence of local failure or the date of death. LC was defined as the absence of local tumor progression including all cases of stable response.

Continuous variables are expressed as the medians. Categorical variables are expressed as the frequency and percentage (%). The Kaplan-Meier method was used to estimate time-related censored endpoints. The differences were compared using log-rank statistics. Factors affecting survival were analyzed by Cox's proportional hazards model. All statistical analyses were performed using SPSS 25.0 statistical software (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered as statistically significant.

RESULTS

Data from 73 patients and 81 lesions meeting the inclusion criteria were analyzed. All characteristics of the patients are reported in **Table 1**. Thirty-two of the patients were radiologically compatible with grade 1 meningioma. Forty-four of the patients had undergone previous surgery, pathologically 23 patients were grade 1 and 18 patients were grade 2 meningiomas. After surgery, 18 of them underwent SRS/SRT because of residual disease, while 23 of them underwent SRS/SRT because of recurrence. Forty-six patients were symptomatic and the most common findings were headache and motor loss. The most common localizations were skull base, falx and convexity. The median tumor size was 25 mm (9-59), and the median tumor volume was 6.92 cc (0.7-31.30) 9.92 (0.7-31.30). A median of 12 (12-18) Gy was performed in single fraction, and a median of 18 (18-25) Gy was performed with a median of 3 (2-5) fractions. The median prescription isodose was 83% (77-88).

The median duration of the follow-up period was 49 months (range, 7–138 months). At the end of the follow-up period, 8 patients died, 4 of which were tumor-related deaths. OS had a mean value of 80.06 (95% CI 73.66–86.47) months, median OS could not be achieved (**Figure 1a**). 5- and 7-y OS were 87.6% and 78.9%, respectively. In univariate analysis, gender (p=0.007), number of lesions (p=0.030), and radiosurgery for recurrence (p=0.011) were found to be factors affecting OS (**Figure 1b, 1c, 1d**). In patients with radiosurgery performed for recurrence, 5-y OS was lower than those performed for residual disease and image-diagnosed meningioma (68.3% vs 100% vs 95.2%). 5-y OS were 83.7% and 78.8% for grade 1 and grade 2. Age, location, grade, tumor size, and SRS/SRT were not associated with OS (**Table 2**).

Local recurrence observed in 4 patients and new lesions observed in 2 patients. PFS had a mean value of 81.33 (95% CI 74.73–87.93) months, median PFS could not be achieved (**Figure 2a**). 5- and 7-y PFS were 82.9% and 82.9%, respectively. In univariate analysis, number of lesions (p<0.001), grade (p=0.048) and tumor size (p=0.047) were found to be factors affecting PFS (**Figure 2b, 2c, 2d**). Age, gender, location, and SRS/SRT were not associated with PFS. However, mean PFS was lower in patients who underwent radiosurgery for recurrence than those who underwent primary and residual, but it was not statistically significant (61.51 vs 80.27 vs 85.62 months, p=0.173). In 41 meningiomas of known grade, the 5-y PFS rate was 92.3% in grade 1 meningiomas and 57.9% in grade 2 meningiomas, a statistically significant difference was found (p=0.048). 5-y PFS was found to be 100% in cases with a tumor diameter less than 2 cm, and 71.9% in cases with a tumor diameter greater than 2 cm (p=0.047). Number of lesions (p=0.022) was remained prognostic factor for PFS in the multivariate analysis (**Table 2**).

The tumor control rate was 94.6%. The tumor volume decreased after SRT in 20 patients, remained stable in 49 patients. Tumor progression occurred in 4 patients (5.4%) at a median of 42 months (12-55 months). Response was obtained in the treated lesion in 2 patients, while new lesions were detected outside the initial SRS/SRT area. SRS/SRT was applied to 1 of the newly detected lesions, surgery was performed to the other and 3 of the progressive lesions, and 1 lesion was being followed up. At the last control, it was found that the symptoms were absent or decreased in 17 patients, similar in 21 patients, and worsened in 7 patients.

Table 1. Clinicopathological and Treatment Characteristics

Variable	N (%)	Median (range)
Age		60 (32-87)
Gender		
Female	50 (68.5)	
Male	23 (31.5)	
Location		
Skull base	23 (28.1)	
Falx	17 (20.7)	
Convexity	16 (19.5)	
Others	25 (31.7)	
Symptoms*		
Headache	21 (28.3)	
Motor loss	15 (20.5)	
Visual loss	10 (13.7)	
Hearing loss	2 (2.7)	
Epilepsy	2 (2.7)	
Asymptomatic	26 (35.6)	
Diagnosis		
Image-diagnosed	40 (49.3)	
Pathologically-diagnosed	41 (50.7)	
Pathology		
Grade 1	23 (56.1)	
Grade 2	18 (43.9)	
Number of lesions		
1	60 (82.2)	
>1	13 (17.8)	
Radiosurgery indication		
Primary (Image-diagnosed)	40 (49.3)	
Residue	18 (22.2)	
Recurrence	23 (28.5)	
Size of tumor (cm)		2.5 (0.9-5.9)
Volume of tumor (cc)		9.92 (0.7-31.30)
RT dose (Gy)		
SRS	34 (41.5)	12 (12-18)
SRT	48 (48.5)	18 (18-25)
RT fraction		
1	34 (41.5)	1
>1	48 (48.5)	3 (2-5)
Prescribed isodose		83 (77–88)

RT: Radiotherapy; SRS: Stereotactic radiosurgery; SRT: Stereotactic radiotherapy
* Some symptoms were observed together.

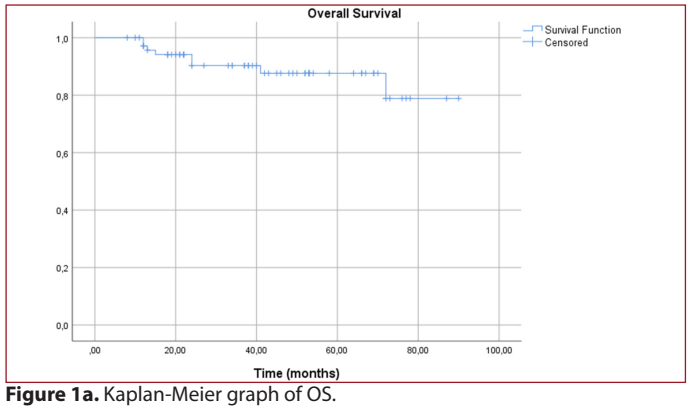

Figure 1a. Kaplan-Meier graph of OS.

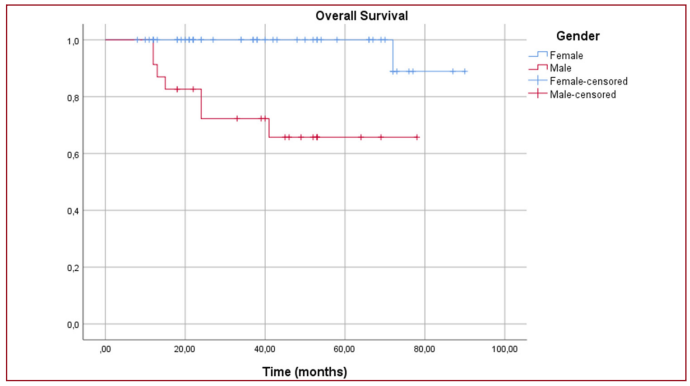

Figure 1b. Kaplan-Meier graph of OS according to gender.

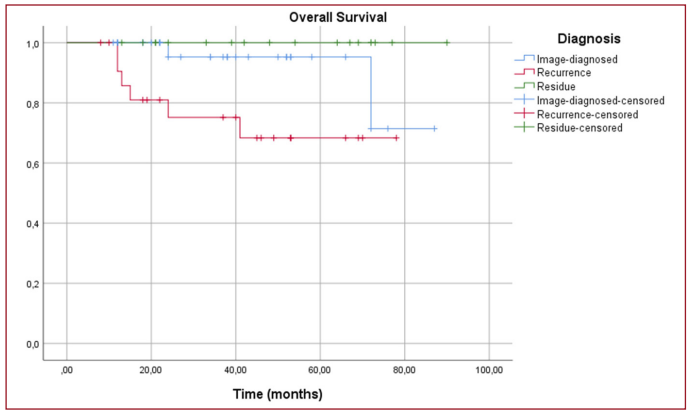

Figure 1c. Kaplan-Meier graph of OS according to diagnosis.

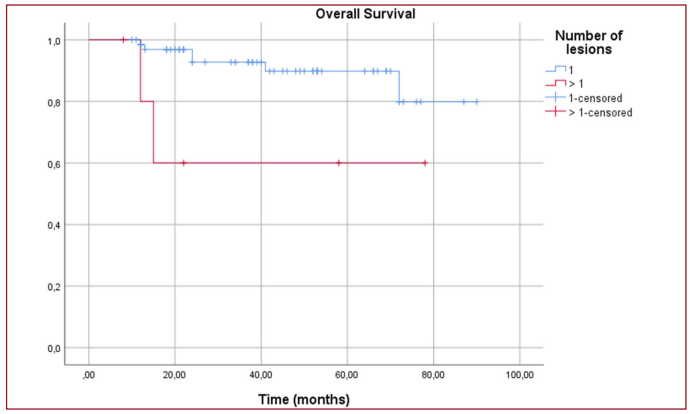

Figure 1d. Kaplan-Meier graph of OS according to number of lesions.

Table 2. Survival Outcomes

Factors	OS				PFS			
	Univariate Analysis				Univariate Analysis			
	Mean	HR (CI 95%)	5-y	p	Mean	HR (CI 95%)	5-y	p
Age								
≤60	83.60	3.44(76.86-90.34)	92.7	0.423	79.88	4.58(70.89-88.80)	78	0.238
>60	63.47	3.90(55.81-71.13)	82.7		69.08	2.69(63.81-74.35)	93.5	
Gender								
Female	88.00	1.88(84.30-96.69)	100	0.007	83.39	3.59(76.35-90.43)	85.6	0.129
Male	58.68	6.03(46.85-70.52)	65.7		66.23	4.12(53.16-69.31)	80.5	
Location								
Skull base	77.75	4.85(68.24-87.27)	90.4		-		100	
Falx	86.50	3.37(79.89-93.11)	92.9	0.511	-		67.9	0.204
Convexity	60.96	7.06(47.12-74.80)	78.6		-		83.9	
Others	57.00	5.80(45.61-68.38)	83.3		-		85.7	
Radiosurgery indication								
Image-diagnosed	-		95.2	0.011	80.27	4.50(71.44-89.39)	87.3	0.173
Residue	-		100		85.62	4.09(77.60-93.64)	87.5	
Recurrence	-		68.3		61.51	4.48(52.71-70.30)	79.7	
Grade								
Grade 1	69.09	4.11(61.03-77.16)	83.7	0.781	70.76	2.14(66.56-74.97)	92.3	0.048
Grade 2	74.77	9.59(55.97-93.57)	78.8		65.67	11.41(43.30-88.04)	57.9	
Tumor size								
<2 cm	78.84	4.83(69.36-88.32)	92.3	0.577	-		100	0.047
≥2 cm	79.37	4.05(71.43-87.31)	85.3		-		71.9	
Number of lesions								
1	81.62	3.20(75.33-87.91)	89.8	0.030	83.85	3.01(77.94-89.76)	87.6	<0.001
>1	52.20	14.13(24.49-79.91)	60		34.00	10.00(14.40-53.60)	0	
Radiotherapy								
SRS	63.74	4.38(55.15-72.32)	80	0.748	69.68	2.27(65.25-74.13)	96	0.418
SRT	80.96	3.78(73.49-88.31)	90.2		79.50	4.32(71.00-87.97)	78.6	
	Multivariate Analysis				Multivariate Analysis			
Gender		7.61(0.94-102)		0.054		-		-
Radiosurgery indication		4.25(0.79-22.80)		0.091		-		-
Grade		-		-		7.99(0.81-78.43)		0.074
Tumor size		-		-		16.46(0.05-422.1)		0.269
Number of lesions		1.89(0.31-11.62)		0.488		8.22(1.34-53.12)		0.022

CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression free survival; SRS: Stereotactic radiosurgery; SRT: Stereotactic radiotherapy

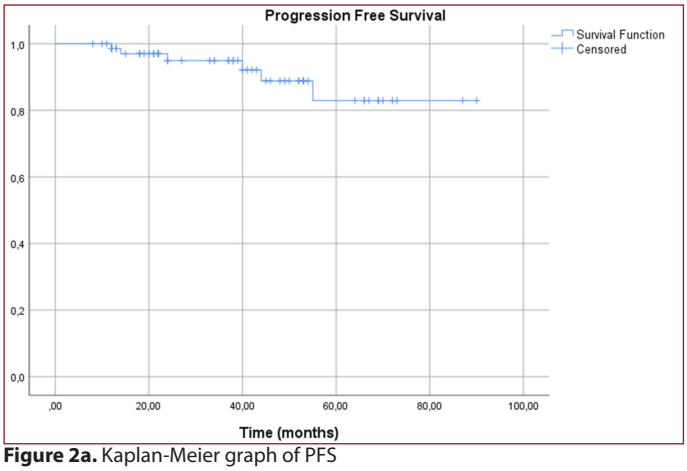

Figure 2a. Kaplan-Meier graph of PFS

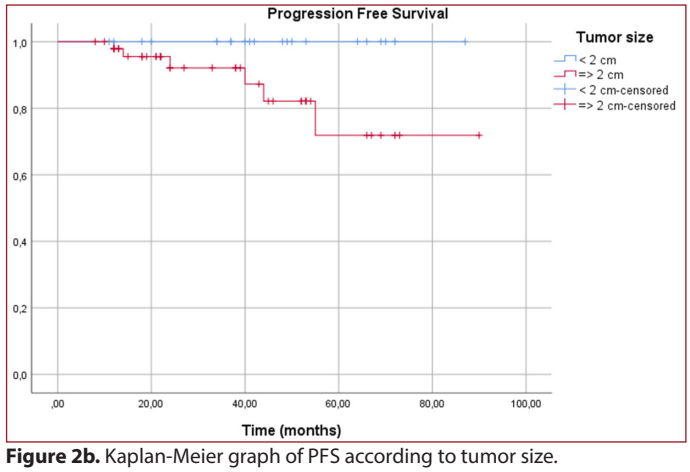

Figure 2b. Kaplan-Meier graph of PFS according to tumor size.

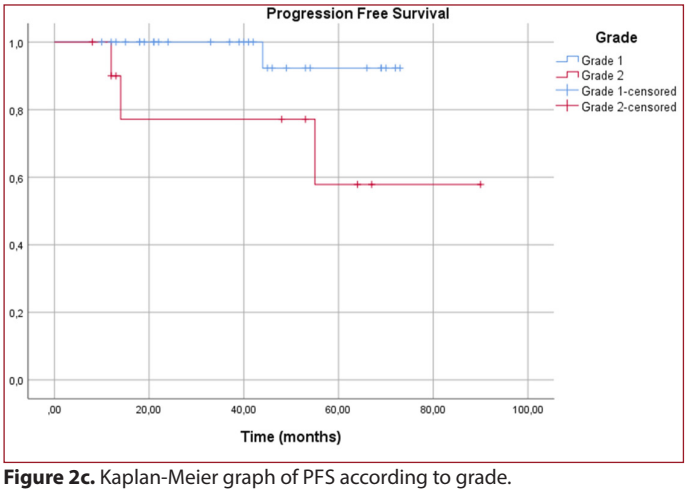

Figure 2c. Kaplan-Meier graph of PFS according to grade.

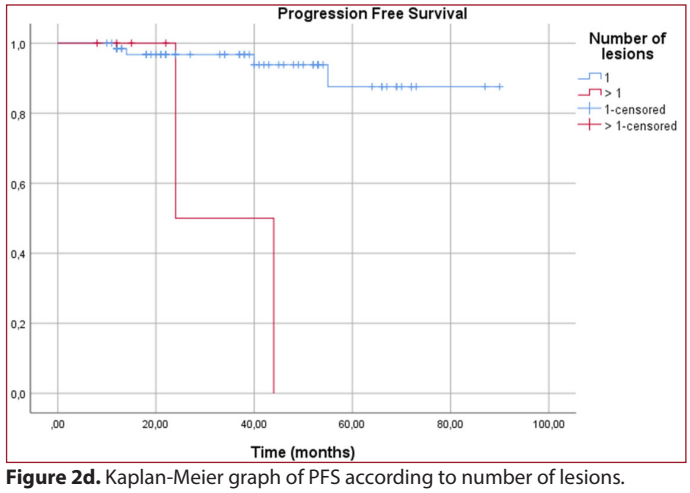

Figure 2d. Kaplan-Meier graph of PFS according to number of lesions.

DISCUSSION

The present analysis aimed to examine the clinical outcomes of SRS/SRT in the treatment of meningioma and to show whether it achieves the main goals, particularly in terms of the possibility of tumor control and the success of preventing progression. It is also aimed to identify factors that may affect clinical outcomes. At a median follow-up of 49 months, we found 5- and 7-y results similar to those in the literature.[5-10] In univariate analysis, it was shown that increasing tumor size and grade negatively affected PFS, radiosurgery due to recurrence adversely affected OS, and increased lesion number negatively affected both.

Previous studies including large series have shown that radiosurgery in benign meningiomas yields LC rates ranging from 85-97% at 5 years.[5-11] In some series with 10-y results, this rate was reported to be between 69-92%.[6-8,11,12] In our study, we found 7-y LC over 94%, we can report that our results are consistent when compared with the results obtained from the literature.

SRS/SRT has long been involved in the treatment of meningiomas. Although the available data are mostly retrospective data, they are considered safe with long follow-up periods. When the studies are examined, it is seen that there is a homogeneous patient population selected according to the diagnosis, surgical status and location, as well as studies belonging to heterogeneous groups in which various parameters are combined. Our study was highly heterogeneous as it included patients with image-diagnosed meningioma who underwent radiosurgery, as well as patients who underwent radiosurgery for post-operative residual or recurrent disease. In 2014, Kondziolka et al.[7] reported that there was no difference in terms of LC and PFS in 290 meningioma cases, of which almost half had undergone previous surgery. In their study, 22 of the patients underwent SRS for relapse and 114 for residual disease. The authors did not report a difference in OS in relapsed patients, but in our study, worsened OS was detected in patients who underwent SRS/SRT for relapse. In addition, although it was not statistically significant in our study, PFS rates were shown to be lower in relapsed patients than in others.

In fact, grade I meningiomas are more frequently included in SRS/SRT studies due to their high incidence. These lesions have been image-diagnosed, it is difficult to distinguish them from malignant meningiomas except for some special imaging techniques, but these imaging techniques are not included in routine applications.[13] On the other hand,

we encounter series that include patients with a history of surgery who underwent radiosurgery due to recurrence or residue. Such studies allow a more accurate assessment of the relationship between meningioma grade and survival outcomes. Low grade patients were included in some of the studies in which SRS/SRT was applied due to postoperative residue or recurrence, but we also come across a limited number of studies in which grade 2 or even grade 3 patients were added.[9] In this context, it was emphasized that PFS worsened with increasing grade in a retrospective series.[7] Grade 2 meningiomas constituted a quarter of the patients included in our study. Similarly, PFS was shown to be adversely affected in grade 2 cases. In another study, SRS was applied to 75 grade 2 meningioma cases due to postoperative residual or recurrence.[14] The 5-y OS was determined as 81.1% and the 5-y PFS as 55.7%. In our study, the 5-y PFS was found to be similar to this study with a rate of 57.7%, but no difference was found in terms of OS according to grade.

Another important parameter affecting the treatment response is the size or volume of the tumor, which has been emphasized in many studies.[6,15] Manabe et al.[15] reported that tumor size <3 cm (<13.5 ml) had a better PFS, and tumor control was difficult in patients with a tumor size greater than 3 cm. Dibiase et al.[6] reported that both OS and PFS were significantly worse in patients with tumor volume above 10 cc. In our study, a positive correlation was shown between tumor diameter less than 2 cm and PFS. Furthermore, in a very large retrospective study involving 4565 patients, it was reported that PFS decreased if the number of lesions was greater than 1.[8] We also found that the number of lesions affected both OS and PFS in our study, and we found that it remained prognostic for PFS in the multivariate analysis.

While applying SRS/SRT, the questions of whether it is a single fraction or multiple fractions and which patient, have been one of the main subjects of the studies as well as in our daily practice. In the meta-analysis published in 2022, which included 20 studies and over 1400 patients, it was observed that 5-y results did not change when single fraction and multiple fractions schemes were compared.[16] In our study, no difference was observed in terms of OS and PFS with single or multi-fractionated RT. In our study, the main reason for the preference of multi-fraction treatments was the presence of larger tumors and tumors close to critical structures, as in other studies.

Unfortunately, there are limitations of our study. Despite the 5- and 7-year results, the study was highly heterogeneous. One reason for this was the inclusion of patients with image-diagnosed meningioma who underwent radiosurgery, as well as patients who underwent radiosurgery for post-operative residual or recurrent disease. Another reason is that both grade 1 and grade 2 patients were included and the grade of meningioma was not included in the study inclusion criteria. Also, its retrospective design may lead to the possibility of selection bias. Due to its retrospective nature, symptomatic response and treatment-related toxicity assessment could not be defined in detail, although complaints were recorded during the follow-up period.

CONCLUSION

Since SRS/SRT can provide high tumor control in the management of meningioma, it can be preferred as an alternative treatment method, especially in patients who are diagnosed radiologically, who are not candidates for surgery or who refuse surgical treatment, as well as in cases of residual and recurrence in the post-surgical period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by The University of Health Sciences, Samsun Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (No:2021/12/3, Date:23.6.2021)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

What Is the Effectiveness of the Home Exercise Program on Dyspnea after Mild-Moderate COVID-19 Pneumonia?

Hafif-Orta Derecede COVID-19 Pnömonisi Sonrası Ev Egzersiz Programının Dispne Üzerine Etkinliği Nedir?

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Abstract

Aim: The aim of this study was to investigate the efficacy of a home-based breathing exercise program on dyspnea, quality of life, depression and sleeping disorders in patients with COVID-19 pneumonia after discharge from the hospital.

Material and Method: The study was completed with a total of 60 participants. The intervention group (n=39) received a homed-based exercise program including controlled breathing techniques and low-intensity upper and lower extremity exercises. The control group (n=21) did not receive any intervention. The patients were evaluated with the Modified Borg Scale (MBS), Nottingham Health Profile (NHP), Insomnia Severity Index (ISI) and Beck Depression Inventory (BDI) before and at the end of the intervention.

Results: After treatment, the MBS scores significantly decreased in both the intervention and control groups compared with the baseline values ($p<0.05$). There was a statistically significant difference before and after the treatment when the MBS scores were compared between the groups ($p<0.001$). The changes in the post-treatment BDI, NHP and ISI scores compared to the baseline did not significantly differ between the two groups.

Conclusion: This study showed that home exercise program after COVID-19 pneumonia was significantly effective in relieving dyspnea, but not as effective in improving quality of life and sleep and depression complaints.

Keywords: COVID-19, pneumonia, exercise, dyspnea

Öz

Amaç: Bu çalışmanın amacı COVID-19 pnömonisi tanılı hastalarda hastaneden taburcu olduktan sonra evde uygulanan solunum egzersiz programının dispne, yaşam kalitesi, depresyon ve uyku bozuklukları üzerine etkinliğini araştırmaktır.

Gereç ve Yöntem: Çalışma toplam 60 katılımcı ile tamamlandı. Müdahale grubu (n=39), kontrollü nefes alma teknikleri ve düşük yoğunluklu üst ve alt ekstremite egzersizlerini içeren ev egzersiz programı aldı. Kontrol grubuna (n=21) herhangi bir müdahale uygulanmadı. Hastalar tedavi öncesi ve sonrasında Modifiye Borg Ölçeği (MBÖ), Nottingham Sağlık Profili (NSP), Uykusuzluk Şiddet İndeksi (UŞİ) ve Beck Depresyon Envanteri (BDE) ile değerlendirildi.

Bulgular: Tedaviden sonra, başlangıç değerlerine kıyasla hem müdahale hem de kontrol gruplarında MBÖ puanları önemli ölçüde azaldı ($p<0.05$). Gruplar arasında MBÖ skorları karşılaştırıldığında tedavi öncesi ve sonrası istatistiksel olarak anlamlı fark vardı ($p<0.001$). Tedavi öncesi ve tedavi sonrası BDE, NSP ve UŞİ skorlarındaki değişiklikler ise, iki grup arasında anlamlı farklılık göstermedi.

Sonuç: Bu çalışma ile COVID-19 pnömonisi sonrası ev egzersiz programının dispneyi azaltmada etkili olduğu gösterilirken, yaşam kalitesini, uyku bozukluğunu ve depresyon şikayetlerini iyileştirmede etkisinin anlamlı düzeyde olmadığı gösterilmiştir.

Anahtar Kelimeler: COVID-19, pnömoni, egzersiz, dispne

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INTRODUCTION

Coronavirus is a single-stranded RNA virus which cause diseases ranging from the common cold to more serious clinical manifestations.[1] This pathogen, identified by World Health Organization (WHO) as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in January 2020, has a high risk of transmission and causes bilateral interstitial pneumonia, resulting mortality in progressive cases. The resulting disease associated with this virus has been defined as COVID-19.[2] Per National Health Institutes, disease severity is classified into five levels as asymptomatic or presymptomatic infection, mild illness, moderate illness, severe illness, and critical illness.[3] COVID-19 particularly affects the respiratory system and causes dyspnea. Also physical and psychological negative effects of immobility due to hospitalization are seen in patients with COVID-19 pneumonia. In addition, most patients may have muscle pain and fatigue and accompanying pulmonary[4] and musculoskeletal system symptoms and changes in their mood and quality of life.

The guidelines for the management of acute and subacute process after SARS-CoV-2[5] recommends a rehabilitation program (first in the hospital accompanied by a physiotherapist, followed by a home program, tele-rehabilitation, etc.) in the post-discharge period after the evaluation of the physical, functional, cognitive and psychosocial losses of the patient related to COVID-19. In patients with mild or moderate symptoms, rehabilitation exercises have been shown to improve respiratory system function and relieve muscle pain. Studies have shown that medical treatment, rehabilitation (including joint range of motion exercises) and exercise prescriptions including pulmonary exercises have positive effects on the respiratory and cardiovascular system endurance and quality of life, sleep patterns, and depression after COVID-19 pneumonia.[6-9]

In this study, we aimed to show the effects of a home-based exercise program on dyspnea, sleep, mood and quality of life in patients who had received treatment for COVID-19 pneumonia.

METHODS

This was a quasi-experimental study where participants were assigned to either the intervention group (IG) or control group (CG) without random assignment. All the patients acknowledged their understanding and willingness to participate by providing signed consent. The study was conducted between and February 2021 and August 2021 at Kutahya Health Sciences University Hospital, Turkey. Approval for the study was granted by the Clinical Research Ethics Committee of the university (date/number: 30.12.2020/2020-08/05). The methods used in this study were reported using the TREND statement.

Participants

Recruitment and setting: Patients who were followed up with a diagnosis of mild to moderate COVID-19 and completed their treatment in the hospital during the study period were screened for eligibility by an independent physician and subsequently invited to participate in the study. All the participants were informed in advance about the procedures and assessments to be performed in the study, and those who agreed to participate in the study signed the consent form.

Inclusion criteria

- Age between 20 and 50 years
- Mild-moderate COVID-19 diagnosis
- Completing medical treatment for COVID-19
- Oxygen saturation above 95% at the time of discharge
- Not be vaccinated

Exclusion criteria

- Being uncooperative
- Presence of an additional chronic systemic disease
- Uncontrolled hypertension
- Vision or hearing problem
- Diagnosis of advanced heart or lung disease for which exercise is contraindicated
- Cognitive disorders
- Being immobile

Study procedures

After determining the IG and CG groups, the participants were evaluated by a blinded researcher (M.A.L.), and then home-exercise were planned by a different researcher (F.Y.). They were reevaluated by the same blinded researcher (M.A.L.) at the end of the eight weeks. The participants in IG received an exercise program including breathing techniques and low-intensity upper and lower extremity exercises while CG did not receive any intervention.

Intervention

Exercise program: Before discharge, the patients in IG underwent 30 minutes of training and exercises under the supervision of a researcher with eight years of experience. Training was planned as controlled breathing techniques, methods to alleviate shortness of breath, and low-intensity upper and lower extremity exercises. Patient education included diaphragmatic breathing and pursed-lip breathing as controlled breathing techniques. The home exercise program recommended by WHO was used for low-intensity upper and lower extremity exercises after hospital discharge. This program included warm-up exercises, shoulder shrugs, shoulder circles, side bends, knee lifts, ankle taps, and ankle circles. As conditioning and strengthening exercises, stepping in place, climbing stairs, walking in place, sitting and standing, push-up on the wall and quadriceps isometric exercises were given. Each exercise was planned to be undertaken 10 times twice a day

for five days a week. The patients were also provided with an explanatory visual form that showed how to perform each exercise.

Outcomes

Data regarding the participants' age, gender, height, body weight, body mass index,and education level were recorded on a previously prepared assessment form during face-to-face interviews. The participants' dyspnea, quality of life, sleeping disorders and depression were then assessed using the methods described below. All the assessments were repeated before and after treatment by the same physician (A.O.) who was blinded to the interventions. Quality of life was the primary outcome measure, and sleeping disorders and depression were the secondary outcome measurements.

Assessment of Dyspnea

The Modified Borg scale, consisting of 10 items describing the severity of dyspnea at rest and during exercise, was used to assess dyspnea. This scale was developed by Borg in 1970 to measure the effort spent during physical exercise. It is frequently used to evaluate the severity of dyspnea during exertion and at rest.[10]

Assessment of Quality of Life

The Nottingham Health Profile (NHP) is a subjective scale that determine show patients perceive their illness. In the first part consisting of 38 items, the following six domains are evaluated: energy level, pain, emotional responses, sleep, social isolation, and physical abilities. The questions in the scale are answered as "Yes" or "No" and scored between 0 and 100. An increase in the score indicates an increase in distress experienced by the patient. The second part of the scale is optional and contains seven questions related to work, housekeeping, social life, personal relationships, sexual life, hobbies and interests, and holidays. The questions are scored between 0 and 1, givinga total of 7 points. In this study, the Turkish version of NHP was used. The validity and reliability studies of this version were undertaken by Kucukdeveci et al.[11]

Assessment of Depression

The depression levels of the participants were evaluated using the Beck Depression Inventory (BDI) consisting of 21 questions. Each question has a set of at least four possible responses (0-3), ranging in intensity. According to the total scores obtained, 0-9 is considered normal, 10-19 mild depression, 20-30 moderate depression, and 31-63 severe depression. The validity and reliability of the Turkish version of BDI were shown by Ulusoy et al.[12]

Assessment of Sleeping Disorders

The severity of the insomnia problems of the patients were evaluated with the Insomnia Severity Index (ISI), which measures difficulties in transition to sleep, difficulties in maintaining sleep, waking up very early, satisfaction from sleep patterns, impairments in daily functioning, detect ability of sleep-related disturbances, and the level of stress caused by sleep problems. The scale consists of seven items scored from 0 to 4. The total score that can be obtained from the scale ranges from 0 to 28. The validity and reliability of the Turkish version of ISI were demonstrated by Boysan et al.[13,14]

Sample Size

The sample size calculation was performed with the G*Power version 3.1.9 software. (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) based on the results of Gonzalez-Gerez et al.[15] The power analysis results were considered for sample calculation using a one-sided hypothesis test with independent samples t-test with a confidence of 95%, power of 80%, alpha of 5%, and effect size of 0.650. As a result of the analysis, 60 patients were required.

Randomization

Randomization was carried out by a different researcher (G.B.), who was not involved in the application of interventions or evaluation of outcomes. Patients to be assigned to IG or CG were selected by simple randomization with a 1:1 allocation ratio according to a list generated by an online randomizer. Opaque and sealed envelopes were used to conceal the allocation before the intervention

Blinding

The principal investigator was blinded to the group allocation during assessment, and was not involved in the data analysis process. The participants were asked not to provide any information about their group allocation to the responsible researcher (M.A.L.) who made the assessment.

Statistical Analyze

The Statistical Package for the Social Sciences (SPSS, IBM, Armonk, NY, USA), version 21.0 was used for statistical analyses. Descriptive data were given by calculating mean, frequency distribution, minimum, maximum, standard deviation, and percentage values. The conformity of the variables to the normal distribution was examined with the Kolmogorov-Smirnov/Shapiro-Wilk test. Student's t-test was used to compare the differences between the groups in the pre-treatment and post-treatment evaluations in both groups, and $p<0.05$ was accepted as the statistical significance level.

RESULTS

The study was completed with a total of 60 participants (41 female, 19 male). There were 39 patients (42.74±14.24 years) in IG and 21 patients (41.76±11.30 years) in CG. Age, gender, body mass index, education levels and smoking status of the individuals participating in the study are shown in **Table 1** by groups. In the comparison of the demographic data of the patients included in our study, no statistically significant difference was found.

Table 1. Demographic characteristics of the groups

	Intervention Group (n=39) (Mean±SD)	Control Group (n=21) (Mean ±.SD)	p value
Age (years)	42.4±14.24	41.76±11.30	0.786
BMI (kg/m2)	27.12±4.74	26.31±4.66	0.530
Sex	**n (%)**	**n (%)**	
Male	13 (33.3)	6 (28.6)	0.705
Female	26 (66.7)	15 (71.4)	
Smoking	**n (%)**	**n (%)**	
+	6 (154)	1(4.8)	0.222
-	33 (84.6)	20 (95.2)	
Education	**n (%)**	**n (%)**	
Illiterate	0	0	
Primary school	6 (15.4)	5 (23.8)	0.722
Middle school	8 (20.5)	4 (19.0)	
University	25 (64.1)	12 (57.1)	

BMI: Body mass index , SD: Standart deviation, *p < 0.05

Primary Outcomes

There were no significant differences between the groups in terms of the MBS scores before treatment (p=0.936). The post-treatment MDS scores significantly increased in both IG and CG after treatment compared to the baseline (p<0.001), but there was a significant difference between the groups (p<0.001) (**Table 2**).

Table 2. Baseline and post-treatment MBS scores of the groups

	Intervention Group (n=39)		Control Group (n=21)		z	p
	(Mean±SD)	Min-Max	(Mean±SD)	Min-Max		
Baseline MBS	3.79±0.46	4 (3-5)	3.80±0.513	4 (3-5)	405,5	0,936
Post-treatment MBS	0.94±0.51	1 (0-2)	2.80±0.51	3 (2-4)	12,50	<0.001
p	<0,001		<0,001			

SD: Standart deviation, MBS: Modified Borg Scale, z: Mann Whitney U Test, *p < 0.05

Secondary Outcomes

There were no significant differences between the groups in terms of the NHP (part 1) scores before treatment (250.69±147.78in IG and 243.73±177.72 in CG, p=0.846). The post-treatment NHP (part 1) scores significantly increased in both groups (p<0.001), and there was no significant difference between IG and CG (p=0.395) **Table 2**).The pre-treatment NHP (part 2) scores did not significantly differ between IG and CG (in IG 3.79±2.66 and 2.76±2.83, respectively, p=0.203). The post-treatment NHP (part 2) scores significantly increased in both IG and CG compared to the baseline (p=0.003 and p<0.001, respectively), and there was no significant difference between the groups (p=0.06) (**Table 3**).

There were no significant differences between the two groups in terms of the pre-treatment ISI scores (11.21±6.55 in IG and 9.76±6.53 in CG, p=0.566). The post-treatment ISI scores significantly increased in both groups compared to the baseline (p<0.001). In addition, no significant difference was observed when the mean differences in the ISI scores between the pre- and post-treatment evaluations were compared between the two groups (p=0.272) (**Table 3**). The pre-treatment BDI scores of the two groups did not significantly differ (20.74±15.46 in IG and 19.10±14.77 in CG, p=0.78). The post-treatment ISI scores significantly increased in both groups compared to the baseline (p<0.001), with no significant difference between the two groups (p=0.174) (**Table 3**).

DISCUSSION

This study evaluated patients diagnosed with mild to moderate COVID-19 pneumonia who received an intervention program including breathing techniques and low-intensity upper and lower extremity exercises. The majority of previous studies in the literature examined the efficacy of pulmonary rehabilitation on respiratory function.[6,16] COVID-19 may

Table 3. Baseline and post-treatment outcome measures of the groups

Variables	Intervention Group (n=39)		Control Group (n=21)		z	p
	(Mean±SD)	Min-Max	(Mean±SD)	Min-Max		
NHP part1 (baseline)	250.69±147.78	234.43 (0-531.92)	243.3±177.72	262.27 (0-602.42)	397	0,846
NHP part1 (after treatment)	61.88±73.27	24.11 (0-244)	91.85±114.03	46.99 (0-401.44)	356	0,395
p	<0.001		<0.001			
NHP part2 (baseline)	3.79±2.66	3 (0-7)	2.76±2.83	2 (0-7)	329	0,203
NHP part2 (after treatment)	0.49±1.45	0 (0-7)	1.10±2.02	0 (0-7)	319,5	0,06
p	0,003		<0.001			
BDI (baseline)	20.74±15.46	18 (0-62)	19.10±14.77	16 (0-56)	391,5	0,78
BDI (after treatment)	4.59±5.72	2 (0-27)	7.19±7.56	4 (0-22)	322,5	0,174
p	<0.001		<0.001			
ISI (baseline)	11.21±6.55	11 (1-28)	9.76±6.53	11 (0-21)	372,5	0,566
ISI (after treatment)	4.62±5.10	4 (0-20)	5.52±4.56	6 (0-13)	339,5	0,272
p	<0.001		<0.001			

SD: Standart deviation, NHP: Nottingham Health Profile, BDI: Beck Depression Inventory, ISI: Insomnia Severity Index, z: Mann Whitney U Test, *p < 0.05

cause changes, especially in the respiratory system, and also the digestive, cardiovascular, musculoskeletal and many other systems.[19] The symptoms of respiratory system are the most obvious and serious, and studies have shown that pulmonary rehabilitation has a positive effect on the quality of life along with the improvement in respiratory function in patients after COVID-19 treatment.[20] We hypothesized that these clinical effects of the breathing exercise would contribute positively to the dyspnea, quality of life, sleep disorders and mood of patients after the completion of medical treatment for COVID-19.

In this study, both patient groups showed improvement in the MBS scores but there were significant differences between the two groups in the post-treatment MBS scores. Dyspnea is one of the most common symptoms after COVID-19, especially in the post-acute disease period. During this period, unless the cause of dyspnea and cough is superinfection (low saturation, newly developed consolidation, fever, and neutrophilia) or pleural inflammation, exercises, especially breathing techniques are effective in treatment.[20] Our study also showed that the exercises given in the post-discharge period significantly reduced the dyspnea scores of the patients similar to the studies in the literature. The time of regression of symptoms after COVID-19 varies. Barman et al. determined that the time until the reduction of symptoms depended on the severity of the disease and other risk factors of the patient.[21] However, a shorter recovery time (e.g.,two weeks) was noted for those with mild/moderate disease. It was also stated that this period could extend up to three months or even longer in cases with severe findings.[22] In this context, although exercise was not given to the control group, the reason for the decrease in dyspnea symptoms in that group may be due to the decrease in the effects of COVID- 19 pneumonia after discharge and the regression of the inflammatory period of the disease.

In the current study, both patient groups had improved NHP scores after treatment and there was no significant difference between the groups in relation to the total post-treatment NHP scores. The improvement in the NHP scale, which evaluates energy level, pain, emotional responses, sleep, social isolation, physical abilities and daily life activities shows that both respiratory and range of motion exercises are effective in recovery. However, in a previous study investigating the effects of exercise among 72 patients with a diagnosis of COVID-19, a significant improvement was found in quality of life in the pulmonary rehabilitation group compared to the control group receiving no rehabilitation intervention.[19] In contrast, in our study,the absence of a significant difference between IG and CG in relation to the improvement in pneumonia and other symptoms after discharge, as well as quality of life may be due to the exercises not being sufficient and not being regularly undertaken in IG.

There are many studies in the literature showing that exercises performed during the COVID-19 pandemic have a positive effect on sleep problems.[23,24] Previous studies have shown a positive effect of exercise on sleep[9] but this relationship has not been investigated in patients with COVID-19 after treatment. Both our patient groups showed an improvement in the ISI scores but there was no significant difference between the groups after treatment. This result shows that exercise therapy has a positive effect on the improvement of sleep problems, but this does not result in a significant difference, similar to our quality of life data. The reason for the lack of difference between the two groups may be that the patients could not adapt to the exercise program and they performed the exercises without supervision. According to the previous studies, exercise has a beneficial role on depression.[25,26] There are also studies in the literature showing the effectiveness of exercise in relieving depression during the COVID-19 pandemic.[27-29] However, in our study examining the effect of exercise on depression in patients after COVID-19 pneumonia, a significant improvement was found in both the intervention and non-intervention groups. In another study, which examined the effect of exercise on depression symptoms in elderly patients with COVID-19, no significant difference was found between the exercise and control groups[19] which is in agreement with our study. In the current study, we performed the first evaluation in COVID-19 patients immediately after their discharge, which may have been the reason for the high depression scores. COVID-19 pneumonia and hospitalization are factors that can affect the patient's emotional state. The improvement in pneumonia and discharge from the hospital may have positively affected the mood of the patients in both groups.

In our study,the absence of a significant difference between the groups expect in dyspnea may be due to the difficulties experienced by IG in adapting to the exercise program after an active COVID-19 infection, considering that exercises were undertaken at home and only supervised by phone calls. Patients with COVID-19 often have multisystem involvement, which results in lasting effects on quality of life, sleep and mood despite reduced dyspnea. The long-term effects of COVID-19 may also be a reason for the insufficient improvement in the quality of life, mood and sleep problems of patients. Lastly, although dyspnea symptoms improve, there may be other systemic problems associated with COVID-19 that continue in the long term after the resolution of the active infection.[19] These problems can affect patients' mood and cause sleep disorders, and consequently reduce their quality of life.

It may contribute to the literature as it is the first study to investigate the effect of home exercise program on dyspnea, functionality and mood in patients with COVID-19 pneumonia. The limitations of this study include the small sample size, patients not being randomized, and the short follow-up period (two months).

CONCLUSION

Many previous studies have described the efficacy of pulmonary exercises in improving respiratory function in patients after COVID-19 pneumonia. In our study, we considered that breathing techniques would improve respiratory capacity after COVID-19 pneumonia, resulting in an improvement in patients' quality of life and mood. However, at the end of the study, both patient groups were observed to have an improvement with no significant difference between the two. Therefore, in order to demonstrate the superiority of breathing exercises, it is considered that patients should be followed up for a longer period of time. It is also concluded that different results can be obtained from exercise programs implemented by patients under supervision.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kutahya Health Science University Clinical Research Ethic Committee. (Date: 30.12.2020 Decision No: 2020-08/05).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Results of Adjuvant Radiotherapy based on Sedlis Criteria in Early Stage Cervical Cancer

Erken Evre Serviks Kanserinde Sedlis Kriterleri Gözönünde Bulundurularak Uygulanan Adjuvant Radyoterapi Sonuçları

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Abstract

Aim: Investigation of the efficacy of adjuvant radiotherapy (RT) in cervical cancer stage I-IIA according to the International Federation of Gynecology and Obstetrics (FIGO, 2018) in terms of risk factors and oncologic outcomes.

Material and Method: The study included 113 patients with FIGO stage I-IIA. Patients who received adjuvant external pelvic RT and/or intracavitary brachytherapy (ICBT) after surgery retrospectively analyzed for demographic data, histology, grade, tumor size, stage, lymphovascular stromal invasion (LVSI), stromal invasion depth (SID), type of lymphadenectomy, number of dissected pelvic / paraaortic lymph nodes, surgical margin, adjuvant therapies, local relapse, distant failure, overall survival (OS), and progression-free survival (DFS).

Results: After a median follow-up of 160 months, local recurrence was observed in 3 patients, distant metastasis in 6 patients and all-cause death in 15 patients. It was observed that only SID had a statistically significant effect on overall survival among the Sedlis criteria (p=0.04). The ten-year DFS and OS rates were 95% and 94%, respectively .

Conclusions: Promising oncological results were obtained in early stage cervical cancer with adjuvant RT based on Sedlis criteria.

Keywords: Radiotherapy, sedlis criteria, cervix cancer

Öz

Amaç: FIGO (the International Federation of Gynecology and Obstetrics, 2018) Evre I-IIA serviks kanserinde adjuvan radyoterapinin risk faktörleri ve onkolojik sonuçlar açısından etkinliğinin araştırılmasıdır.

Gereç ve Yöntem: FIGO evre I-IIA olan 113 hasta çalışmaya dahil edilmiştir. Cerrahi sonrası adjuvan eksternal pelvik RT ve / ve ya intrakaviter brakiterapi (ICBT) uygulanan hastalar demografik veriler, histoloji, grade, tümör boyutu, evre, LVSI, stromal invazyon derinliği (SID), lenfadenektomi tipi, diseke edilen pelvik/paraaortik lenf nodu sayısı, cerrahi sınır durumu, uygulanan adjuvant tedaviler, lokal relaps, uzak hastalık, genel sağkalım (OS), and hastalıksız sağkalım (DFS) açısından retrospektif olarak incelenmiştir.

Bulgular: Medyan 160 aylık takip sonunda 3 hastada lokal nüks, 6 hastada uzak metastaz, 15 hastada tüm nedenlere bağlı ölüm gözlenmiştir. Sedlis kriterleri içerisinde sadece SID 'ın OS üzerinde istatistiksel anlamlı olarak etkili olduğu gözlenmiştir. (p=0.04). On yıllık DFS ve OS oranı sırasıyla 95% ve 94% olarak bulunmuştur.

Sonuç: Erken evre serviks kanserinde Sedlis kriterlerine dayalı adjuvan RT ile yüz güldürücü onkolojik sonuçlar elde edilmiştir.

Anahtar Kelimeler: Radyoterapi, sedlis kriterleri, serviks kanseri

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INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide and the leading cause of cancer-related deaths.[1] According to the 2018 revised the International Federation of Gynecology and Obstetrics (FIGO) staging system, Stage I-IIA, which is limited to the cervix and uterus, is defined as early stage disease and accounts for approximately 50-75% of all cervical cancer patients.[2]

The indication for postoperative radiotherapy in early stage cervical cancer is determined by the stage of the disease and the risk factors associated with recurrence. High risk factors include positive surgical margin, lymph node metastasis, presence of parametrial invasion; while medium risk factors include tumor size, presence of lymphovascular stromal invasion (LVSI), cervical stromal invasion defined as Sedlis criteria.[3-7]

Studies are still ongoing on which adjuvant treatment or treatment combinations should be applied in the presence of different risk factors in early stage cervical cancer. Answers to questions such as in which patients chemotherapy (CT) should be combined with RT, in which subgroup vaginal brachytherapy alone may be sufficient, in which groups vaginal brachytherapy may contribute to external pelvic RT are still being sought.[8]

Sedlis criteria were developed to predict recurrence based on data from patients with SCC histology. However, research is ongoing on different biomarkers and nomograms, including other histologies and other factors, which may help in the selection of adjuvant therapy for early stage disease.[9-12]

Therefore, in this study, we aimed to share adjuvant treatments and oncologic outcomes in patients with early stage cervical cancer without lymph node metastasis according to the current FIGO (2018) staging system.

MATERIAL AND METHOD

Study Population

Among the patients who admitted to our center with the diagnosis of cervix cancer between 2000 and 2020, patients with stage I-IIA were evaluated retrospectively. The study included 113 patients who underwent adjuvant external pelvic RT and/or intracavitary brachytherapy (ICBT) after surgery. Patients with lymph node metastases or parametrial invasion were excluded from the study.

All patients were evaluated for demographic data, histology, grade, tumor size, stage, LVSI, stromal invasion depth (SID), type of lymphadenectomy, number of dissected pelvic / paraaortic lymph nodes, surgical margin, adjuvant therapies, local relapse, distant failure, overall survival, and progression-free survival. Patients were staged according to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO 2018).[13] The study was carried out with the permission of Istanbul Prof. Dr. Cemil Tascioglu City Hospital. Ethics Committee (Date: 23.01.2023, Decision No: E-48670771-514.99-20792411)

Statistical Analysis

The data for continuous variables were expressed as the median (range), and categorical variables were reported as number and percentage. Data distribution was assessed by the Kolmogorov–Smirnov test. In consideration of the sample size, the non-normal distribution of variables was assumed, and nonparametric tests were used for between-group comparisons. So, the Mann–Whitney U test for continuous variables, and the Chi-square test for categorical variables were used. Kaplan-Meier curves were generated for OS and DFS, and significance was assessed using the log-rank test. Statistical analyses were performed using SPSS 25 software (SPSS Inc., Chicago, IL, USA). A probability value of $p<0.05$ was considered significant.

RESULTS

Patient Characteristics

The median age of the patients was 49 (range, 30-72). Median follow-up was 160 (range, 6-275) months. 82% of patients had squamous cell histology. The baseline characteristics of the patients are presented in **Table 1**. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO). The median tumor size was 3.5 cm (range: 0.5-9.5) and patients with a tumor size of 4 cm or more were 36.3%.

Table 1: Patient and tumor characteristics

	Patients (n:113,%)
Age	Median; 49 (range 30-72)
<40 yr	20 (17.7%)
40-59 yr	76 (67.3%)
≥60 yr	17 (15%)
Histology	93 (82%)
Squamous cell	15 (13.3%)
Adenocarcinoma Adenosquamous	4 (3.7%)
Clear cell	1 (1%)
Tumor grade	
G1	35 (31%)
G2	55 (48.7%)
G3	23 (20.3%)
Tumor Size	
<4 cm	72 (63.7%)
≥4 cm	41 (36.3%)
FIGO Stage	
I (A/B)	94 (83.2%)
IIA	19 (16.8%)
LVSI	
Negative	59 (52.2%)
Positive	54 (47.8%)
Stromal Invasion Depth	
Superficial	29 (25.7%)
Medium	41 (36.3%)
Deep	43 (38%)
Surgical margin	
Negative	103 (91.2%)
Positive	10 (8.8%)

The rate of patients who did not undergo LND was also 36.3%. Surgical margins were positive in 10% of the patients. Cisplatin based concomitant chemoradiotherapy were given of% 40 and all patients underwent postoperative pelvic external RT and/or ICBT. The median dose of external RT administered was 46 Gy (45-50.4 Gy) and median ICBT dose was (15-30 Gy). Adjuvan treatment details are presented in **Table 2**.

Table 2: Treatment Details

	Patients (n:113,%)
Lymphadenectomy	
Only pelvic	49 (43.4%)
Pelvic + paraaortic / Paraaortic sampling	23 (20.4%)
None	41 (36.3%)
Number of LNs removed (median, range)	
Number of pelvic LNs removed	Median; 12 (range 1-49)
Number of paraoartic LNs removed	Median; 6 (range 1-25)
Chemotherapy	
No	73 (64.6%)
Yes	40 (35.4%)
Radiotherapy	
Whole pelvic RT	28 (24.8%)
Whole pelvic RT + Brachytherapy	74 (65.5%)
Only Brachytherapy	11 (9.7%)

Oncological Results

After a median follow-up of 160 months, local recurrence was observed in 3 patients, distant metastasis in 6 patients and all-cause death in 15 patients. The effects of age groups (<40 yr, 40-59 yr, ≥60 yr), pretreatment hemoglobin level, tumor size above/under 4 cm, SID, number or type of pelvic dissected LNs, stage, surgical margin status and presence of LVSI on OS were analyzed. Among these parameters, only SID had a statistically significant effect on OS. (p=0.04). The ten-year DFS and OS rates were 95% and 94%, respectively (**Figure 1-2**).

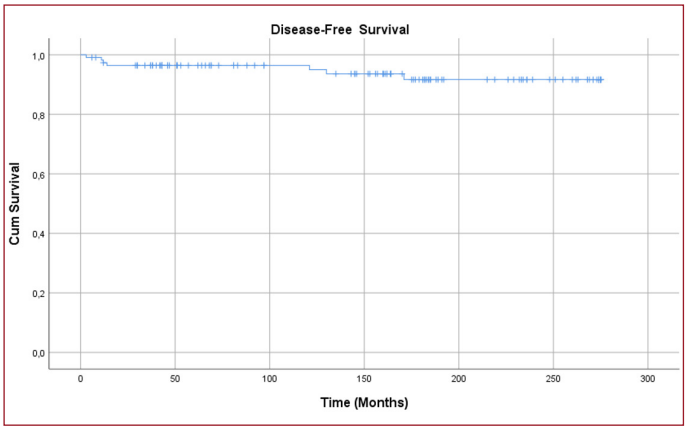

Figure 1. Kaplan-Meier plots of disease free survival.

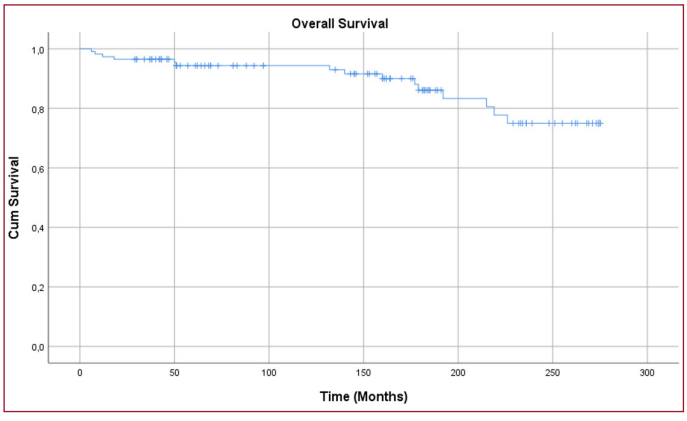

Figure 2. Kaplan-Meier plots of overall survival.

DISCUSSION

A significant number of studies examining the role of adjuvant therapy in early stage cervical cancer were conducted according to the FIGO 2009 staging criteria and included lymph node positive patients.[14-16] The patients in our study were staged according to the current FIGO staging system, which was revised in 2018 and included pelvic/paraaortic lymph node involvement in the staging. Therefore, it does not include lymph node positive patients. However, there was no effect of whether pelvic/ paraaortic dissection was performed or the number of lymph nodes dissected. The reason for this was thought to be that 90.5% of the patients in the study underwent pelvic +/- ICBT. When analyzed according to Sedlis criteria, no effect of tumor size >4 cm or presence of LVSI on OS was shown in our study. The only effective factor on OS was found to be SID.

Rotman et al. investigated the role of postoperative RT in a Phase 3 randomized trial involving 277 patients with stage 1B. They found that postoperative external RT reduced the risk of recurrence, progression or death in patients with two or more risk factors such as LVSI (+), stromal invasion deeper than 1/3 and tumor diameter greater than 4 cm (p=0.007 and p=0.009 respectively).[17]

Gan et al. retrospectively evaluated 221 patients who underwent hysterectomy for early stage cervical cancer. They observed a statistically significant increase in 3-year local recurrence-free survival (LRFS) in patients who received adjuvant RT compared to surgery alone.[18]

Solis et al. analyzed the data of 28 patients who underwent adjuvant small pelvic field radiotherapy without brachytherapy or chemotherapy for intermediate risk. They reported OS, DFS and LRFS as 100%, 82% and 86% respectively at a median follow-up of 41 months. They also stated that small pelvic area RT is a tolerable and safe treatment with any grade 3-4 GIS/GUS toxicity.[19] In our study, no difference was observed between patients who received pelvic RT only, ICBT only or external pelvic RT and ICBT together.

Fabrini et al. analyzed the role of postoperative RT in 51 patients with clinical FIGO stage 1B cervical cancer. It was observed that 56% of patients received concomitant CT and 64% received brachytherapy. At a median follow-up of 58 months, the 5-year DFS and OS rates were 74.9% and 82.0%, respectively.[20]

GUO et al. compared the results of adjuvant RT and adjuvant chemoradiotherapy (CRT) treatment in early stage cervical cancer through a meta-analysis. In the evaluation of 3601 patients, it was observed that similar results were recorded in terms of RT vs CRT in the presence of a single risk factor, but better recurrence-free survival results were obtained in the CRT arm in the presence of multiple risk factors.[21] In our study, 18% of the patients had non-SCC histology and 10% of the patients were surgical margin positive patients with high risk factors. ICBT with external pelvic RT was performed in 65% of patients and concurrent CT in 40% of patients. We did not observe any effect of CT on disease-free survival or OS.

In a Phase 3 randomized trial, Huang et al. examined the effect of sequential or concurrent CT administration on DFS compared to RT alone in early-stage cervical cancer. 1048 patients were randomized into 3 arms: RT alone, sequential CT-RT and concurrent CRT as adjuvant treatment after surgery. No difference was observed between the concurrent CT arm and the RT alone arm. However, they observed a decrease in the risk of death and an increase in the 3 year DFS and distant DFS rate in the sequential CT-RT arm compared to the other arms.[22]

Nie et al. retrospectively analyzed 596 patients with FIGO (2018) Stage I-IIA according to whether they received adjuvant therapy. With a median follow-up of 62 months patients were evaluated according to adjuvant CT alone, RT alone, concurrent CRT and observation arms. They claimed 5-year PFS (progression-free survival) rates of 93.9%, 93.4%, 91.6%, 74.6% and 5-year OS rates of 93.9%, 93.4%, 92.4%, and 76% respectively. They observed that OS and PFS rates were better in patients who received adjuvant therapy than in those who did not, and PFS and OS rates were lower in the RT alone arm than in the CT alone arm and in the CRT arm ($P<0.05$). They also reported no difference between patients with a single or multiple risk factors.[23]

Xiao-Li Yu et al. compared the two groups that received and did not receive brachytherapy with external pelvic RT in adjuvant treatment in two hundred and twenty-five patients with early-stage operated cervical cancer. It was observed that the 5-year local regional recurrence-free survival rates were statistically significantly higher in the brachytherapy group. It was also emphasized in the study that the indication for brachytherapy treatment with pelvic RT could be determined by considering more factors.[24]

CONCLUSION

Adjuvant external pelvic RT+/- ICBT in early-stage cervical cancer has shown very good ten year OS and DFS results. Large-scale randomized trials are needed for modeled adjuvant treatment selection according to subgroups.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Prof. Dr. Cemil Tascioglu City Hospital. Ethics Committee (Date: 23.01.2023, Decision No: E-48670771-514.99-20792411)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article / Orijinal Araştırma

Effect of the Single-Layer and Double-Layer Closure on Residual Myometrial Thickness, Isthmocele Occurrence, and Gynecological Disorders: A Prospective Randomized Controlled Study

Tek Kat ve Çift Kat Onarımın Rezidüel Miyometriyal Kalınlık, İstmosel Oluşumu ve Jinekolojik Bozukluklar Üzerine Etkisi: Prospektif Randomize Kontrollü Bir Çalışma

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Abstract

Aim: Physicians are making great efforts to decrease the long-term complications of the cesarean section such as placental adherent syndromes, uterine scar pregnancies, uterine rupture, abnormal menstrual bleeding, or isthmocele. There is a controversy about the closure technique of the cesarean incision. The purpose of that study was to compare the impact of single layer versus double-layer closure of the hysterotomy incision on the residual myometrial thickness, isthmocele, menstrual disorders, dysmenorrhea, and dyspareunia.

Material and Method: A prospective randomized cohort study has been performed in a tertiary center named Bursa Yuksek İhtisas Training Research Hospital between July – October 2021. Patients were randomly assigned to each procedure (1:1) to the Single Layer Locked Continuous group and Double-layer Continuous un-locked group as uterine closure technique. Patients were examined via transvaginal ultrasound to evaluate the isthmocele occurrence, residual myometrium thickness, and inquired about menstrual properties, dysmenorrhea, and dyspareunia. Patients were also divided into groups via underwent first cesarean and more than one cesarean.

Results: The numbers of the women whose hysterotomy incision was closed by single-layer locked continuous(SLLC) technique and double-layer un-locked continuous(DLUC) technique 68 and 71 respectively. There was no statistically significant difference in terms of demographic variables, obstetric history, post-operative complications, neonatal outcomes. The comparison of these groups revealed that there was no significant difference in terms of post-menstrual bleeding, heavy menstrual bleeding, post-coital bleeding, dysmenorrhea, dyspareunia. The incisional residual myometrial thickness was higher in the DLUC group with a p-value of 0,007. Six patients in SLLC and 5 patients in the DLUC group have detected isthmocele (p: 0,941). Patients have also been categorized as women who undergone their first cesarean section (SLLC n: 33 versus DLUC, n:33) and more than one cesarean section (SLLC n: 35 versus DLUC, n:38). Comparing the patients in these subgroups also did not differ significantly in terms of isthmocele occurrence, menstrual disorders, or residual myometrial thickness.

Conclusion: No significant difference had occurred in terms of isthmocele incidence, or menstrual disorders comparing the single layer versus double-layer closure. However, women whose hysterotomy insicions were closed with double-layer un-locked continuous technique have a thicker resudial myometrium than single layer closure group especially women who underwent repeated cesarean.

Keywords: Single layer, double layer, cesarean, isthmocele, residual myometrial thickness

Öz

Amaç: Klinisyenler sezaryenin plasental yapışık sendromları, uterin skarlı gebelikler, uterin rüptür, anormal adet kanaması veya istmosel gibi uzun dönem komplikasyonlarını azaltmak için büyük çaba sarf etmektedirler. Sezaryen kesisinin kapatma tekniği konusunda bir tartışma mevcuttur. Bu çalışmanın amacı, rezidüel miyometriyal kalınlık, istmosel, adet bozuklukları, dismenore ve disparoni üzerindeki histerotomi insizyonunun tek katmanlı ve çift katmanlı kapatılmasının etkisini karşılaştırmaktı.

Gereç ve Yöntem: Temmuz – Ekim 2021 tarihleri arasında Bursa Yüksek İhtisas Eğitim Araştırma Hastanesi adlı üçüncü basamak bir merkezde prospektif bir randomize kohort çalışması yapılmıştır. Hastalar randomize olarak tek katlı kilitli devamlı onarım ve çift katmanlı kilitsiz devamlı onarım gruplarına ayrılmıştır. Hastalar istmosel oluşumunu, rezidüel miyometriyum kalınlığını değerlendirmek için transvajinal ultrason ile muayene edimiştir ve menstrüel özellikler, dismenore ve disparoni hakkında sorgulanmıştır. Hastalar ayrıca ilk sezaryen ve birden fazla sezaryen uygulanan gruplara ayrılmıştır.

Bulgular: Histerotomi insizyonu tek kat kilitli devamlı (TKKD) ve çift kat kilitsiz devamlı (ÇKKD) teknikle kapatılan kadın sayısı sırasıyla 68 ve 71'dir. Demografik değişkenler, obstetrik öykü, postoperatif komplikasyonlar, neonatal sonuçlar açısından istatistiksel olarak anlamlı fark bulunmamıştır. Bu grupların karşılaştırılmasında adet sonrası kanama, ağır adet kanaması, ilişki sonrası kanama, dismenore, disparoni açısından anlamlı fark olmadığı görülmüştür. İnsizyonel rezidüel miyometrial kalınlık p değeri 0,007 ile ÇKKD grubunda daha yüksekti. TKKD grubunda 6 hasta ve ÇKKD grubunda 5 hastada istmosel saptandı (p: 0,941). Hastalar ayrıca ilk kez sezaryen (TKKD n: 33'e karşı ÇKKD, n:33) ve birden fazla sezaryen (TKKD n: 35'e karşı ÇKKD, n:38) olan kadınlar olarak kategorize edilmiştir. Bu alt gruplardaki hastaların karşılaştırılması da istmosel oluşumu, menstrüel bozukluklar veya rezidüel miyometrial kalınlık açısından anlamlı farklılık görülmemiştir.

Sonuç: İstmosel insidansı veya menstrüel bozukluklar açısından, tek kat ile çift kat kapatma karşılaştırıldığında anlamlı bir fark meydana gelmemiştir. Ancak, histerotomi insizyonları çift kat kilitsiz devamlı teknikle kapatılan kadınlarda, özellikle tekrarlanan sezaryen uygulanan kadınlar, tek kat kapatma grubuna göre daha kalın bir rezidü miyometriyuma sahip bulunmuştur.

Anahtar Kelimeler: Tek kat, çift kat, sezaryen, istmosel, rezidü miyometrial kalınlık

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INTRODUCTION

Cesarean section is the most common surgery in the USA and probably in the whole over the world.[1] The cesarean section used to be performed to save the life of the fetus whether the mother was about to die in ancient times and even considered as a mortal operation till the end of the 19th century.[2] To date, the authors have been discussing the harm of the cesarean delivery which were performed via patients' requests due to the possible complications.[3] The World Health Organization has declared a recommendation that the maximum cesarean rate should not exceed more than 15% whereas the rate was almost more than 30% in most of the countries.[4,5] That recommendation was to avoid the complications such as hemorrhage during the operation, wound site infection, endometritis, or adjacent organs injuries.[6] Besides these issues, the long-term complications could be considered as related to consequent pregnancy complications and pregnancy independent complications. Uterine scar pregnancy, placenta previa, uterine scar rupture or dehiscence, intra-abdominal severe adhesions, and even hysterectomy were the long-term complications of the cesarean section related to concomitant pregnancies.[6-8] Chronic pelvic pain, incisional endometriosis, and cesarean scar defect were complications that were not related to pregnancy.[6,9] Isthmocele which was also called as cesarean scar defect, niche, or pouch, is the disruption of the continuity of myometrium in where the hysterotomy had been performed for the cesarean operation. The symptoms have varied through abnormal uterine bleeding, prolonged bleeding, post-menstrual spotting, menorrhagia, chronic pelvic pain, dysmenorrhea, or even secondary infertility.[10] The healing process of the patient might be the major factor of the formation of isthmocele, however, the dilation of the cervix before the operation, version of the uterus, and operational technique were the other accused reasons. There was no consensus on the closure technique of the hysterotomy scar incision to decrease or prevent the isthmocele process. The purpose of this present study was to evaluate the effect of single-layer locked continuous suture, and the double-layer un-locked continuous suture during cesarean on the formation of isthmocele, menstrual disorders, residual myometrial thickness.

MATERIAL AND METHOD

A prospective randomized cohort study was achieved in Bursa Yuksek İhtisas Training Research Hospital between 1 July – 30 September 2021 after the approval of the Bursa Yüksek Ihtisas Training and Research Hospital Ethical Committee (Project Number: 2011-KAEK-25 2020/06-02)

Women who were admitted to the delivery room were informed about the study and a written informed consult was obtained. Women who had an indication for cesarean delivery and accepted to be a participant were included in the study. The patients were included in the study in a manner of one by one respectively (One patient included in the single-layer suture group, and the next one into the double-layer suture group).

Patients' demographic properties, obstetric history, post-partum events and neo-natal outcomes were recorded. Cesarean section was performed by a resident under the supervision of a gynecologist. Women who had a cervical dilation of above 4 cm, premature rupture of membranes, twin pregnancy, placental anomaly, diabetes mellitus, or known connective tissue disease or immunodeficiency disorder were excluded from the study.

Generally, at the hospital where the study was held, the hysterotomy incisions were closed via single-layer closure technique using locked continuous multi-filament sutures. In the study group where the hysterotomy was closed as a double layer, the incision was closed un-locked and continuous multi-filament sutures. The endometrial edges have been included within the first layer, and the second layer had imbricated the edges of the first layer. The second layer was also un-locked continuous style.

Cesarean section indications, perioperative complications, and postoperative complications have been recorded. Patients were re-evaluated at the post-operative 6th month for isthmocele occurrence. All ultrasonography examinations were performed by the same physician with a Voluson 730 expert (GE Medical Systems) with a 4-9MHz transvaginal transducer probe in the early follicular phase of the menstruation period. Isthmocele has been diagnosed as the existence of an anechoic area at the previous cesarean scar with at least 1 mm depth as Vaate et all described.[11] The measurements have been obtained in the sagittal plane of the uterus. The length and the depth of the isthmocele, the residual myometrium thickness which was measured between scar tissue to the serosa of the uterus. To ensure compatibility with the literature, measurements were made as Stegwee et al described.[12]

The women who underwent the first cesarean section and the women who had the second or more cesarean delivery have been evaluated individually. The primary aim of the study was to expose the effect of the uterotomy closure technique on the occurrence of isthmocele, residual myometrial thickness, menstrual symptoms, and dyspareunia.

Statistical Analysis

The sample size of the study was calculated by using NCSS statistical program by evaluating similar studies.[12,13] (24). To achieve 80% power with 5% type 1 error to detect a minimum clinically significant difference at least 32 individuals must be recruited for each group. The SPSS (version 24) was used to perform the statistical analysis of the study. The normal distribution of the variables was determined by the Shapiro Wilks test. Normally distributed variables were expressed with mean and standard deviation, whereas non-normally distributed continuous variables were expressed as median (minimum-maximum). Mann Whitney U test was used to

compare non-normally distributed continuous variables between two groups while Chi-square or Fisher's exact test was performed for categorical variables. Fisher-Freeman Halton test was used to compare categorical data for more than two groups. An overall p-value of less than 0, 05 was considered a statistically significant result.

RESULTS

The number of patients included in the study was 139. The numbers of the women whose hysterotomy incision was closed by single-layer locked continuously (SLLC) style and double-layer un-locked continuous (DLUC) style were 68 and 71 respectively. The comparison of the major groups which could be assumed as SLLC and DLUC revealed that there was no statistically significant difference in terms of age, body mass index, number of gravidity and parity, previous abortion numbers, and indication of cesarean. The demonstration of the patients' demographic and obstetric characteristics were presented in **Table 1**. The menstrual symptoms and the ultrasonography evaluation of the patients have exposed that there was no significant difference in terms of post-menstrual bleeding, heavy menstrual bleeding, post-coital bleeding, dysmenorrhea, dyspareunia, wound site infection. Although it could be considered clinically non-significant, the incisional residual myometrial thickness was higher (5,3mm versus 5 mm) in the DLUC group with a p-value of 0,007. The evaluation of these parameters was shown in **Table 2**. Six patients in SLLC and 5 patients in the DLUC group have detected isthmocele. The comparison of the groups did not differ significantly. The evaluation of the depth, the width of the isthmocele, and the residual myometrial thickness did not also differ statistically significantly. The demonstration of the ultrasonographic evaluation and comparison of the groups have shown in **Table 3**.

Table 1. Demonstration of the patients' demographic and obstetric characteristics

	Single layer locked continuous Group (n=68)	Double layer un-locked continuous (n=71)	P value
Age (year)	28.7± 5.3	30± 6.1	0.212
Body Mass Index (kg/m²)	26.2 (19.4-41.6)	26.8 (18.6-37.5)	0.836
Gravidity (n)	2 (1-8)	2 (1-6)	0.079
Number of cesarean (n)	2 (1-4)	2 (1-4)	0.892
Indication of cesarean (n) -History of cesarean section -Acute fetal distress - Malpresentation -Macrosomia - Cephalopelvic disproportion - Maternal indications -Others	 33 (48.5%) 13 (19.1%) 5 (7.4%) 6 (8.8%) 8 (11.8%) 3 (4.4%) 0 (0%)	 25 (35.2%) 15 (21.1%) 14 (19.7%) 8 (11.3%) 6 (8.5%) 2 (2.8%) 1 (1.4%)	0.277
Number of previous vaginal birth (n)	0 (0-5)	0 (0-5)	0.043
Previous abortion numbers (n)	0 (0-4)	0 (0-2)	0.281
Birth weight (gram, minumum-maximum)	3370 (2300-4400)	3300 (2500-5000)	0.950
Smoking (n,%)	7 (10.3%)	19 (26.8%)	0.023

Table 2. Comparison of the groups in terms of the symptoms and ultrasonographic evaluation.

	Single layer locked continuous Group (n=68)	Double layer un-locked continuous (n=71)	P value
Post-menstrual bleeding (n,%)	4 (5.9%)	3 (4.2%)	0.715
Heavy menstrual bleeding (>7 days) (n,%)	4 (5.9%)	5 (7%)	1.000
Post-coital bleeding (n,%)	3 (4.4%)	2 (2.8%)	0.676
Dysmenorrhea (n,%)	6 (8.8%)	11 (15.5%)	0.347
Dyspareunia (n,%)	12 (17.6%)	16 (22.5%)	0.612
Wound site infection (n,%)	3 (4.4%)	5 (7%)	0.719
Version of the uterus Anteversion (n,%) Retroversion (n,%)	 55(80.9%) 13 (19.1%)	 56 (78.9%) 15 (21.1%)	0.933
Incisional residual myometrial thickness (milimeter, minumum-maximum)	0.5 (0.30-0.70)	0.53 (0.31-0.69)	0.007

Table 3. Demonstration of the ultrasonographic evaluation and comparison of the groups.

	Single layer locked continuous Group (n=68)	Double layer un-locked continuous (n=71)	P value
Numbers of the women detected isthmocele	6 (8.8%)	5 (7%)	0.941
Depth of isthmocele (milimeter)	2.9 (0.9-3.9)	3.2 (1.4-5.9)	0.792
Width of isthmocele (milimeter)	3.4 (2.6-7)	9 (2.7-10.4)	0.177
Residual myometrial thickness (milimeter)	4.7 (3.2-6.3)	4.3 (3.8-11.2)	0.931

These two groups were also divided into two groups due to the number of cesarean performed. Women who underwent the first cesarean were also divided into two groups as SLLC (n:33) and DLUC (n:33). Patients who had more than one cesarean were also divided into two groups as SLLC (n: 35) and DLUC (n: 38). Comparison of these individually revealed that no statistically significant difference had occurred in terms of demographics variables, obstetrics history, isthmocele occurrence, menstrual disorders, dysmenorrhea, post-coital bleeding, and dyspareunia. Although there was no significant difference in terms of isthmocele incidence, closure of the hysterotomy incision via double layer un-locked continuous technique in the women who underwent repeated cesarean section have thicker residual myometrium. The evaluations of these patients were demonstrated in **Tables 4** and **5**. The technique of the measurements in women with isthmocele and without isthmocele have been demonstrated in **Figure 1** and **2** respectively.

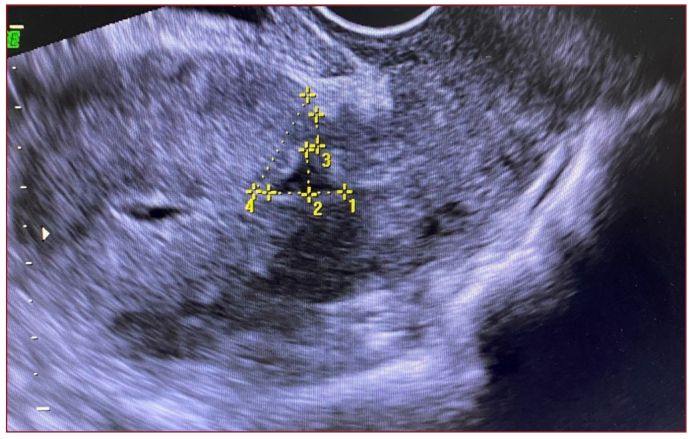

Figure 1. Transvaginal ultrasonographic view of the woman with isthmocele.

isthmocele width
isthmocele depth
residual myometrial thickness
Adjacent Myometrial Tissue

Table 4 Evaluation of the women who had first cesarean section and comparison of these patients by the different closure techniques of the uterus

	First cesarean Single-layer locked continuous Group (n=33)	First cesarean Double layer un-locked continuous (n=33)	P value
Age (year)	27.4 ± 5.2	29.2± 7.1	0.243
Body Mass Index (kg/m²) (kg/m²)	26.1 (20.4-41.6)	25.9 (19.5-34.7)	0.812
Gravidity (n)	1 (1-8)	2 (1-6)	0.214
Previous abortion numbers (n)	0 (0-4)	0 (0-1)	0.964
Birth weight (gram, minumum-maximum)	3413.48 ± 516.73	3528.79 ± 506.42	0.363
Smoking (n,%)	1 (3%)	10 (30.3%)	0.008
Post-menstrual bleeding (n,%)	2 (6.1%)	1 (3%)	1.000
Heavy menstrual bleeding (>7 days) (n,%)	2 (6.1%)	1 (3%)	1.000
Post-coital bleeding (n,%)	0 (0%)	1 (3%)	1.000
Dysmenorrhea (n,%)	2 (6.1%)	3 (9.1%)	1.000
Dyspareunia (n,%)	5 (15.2%)	8 (24.2%)	0.536
Wound site infection (n,%)	2 (6.1%)	3 (9.1%)	1.000
Numbers of the women detected isthmocele	2 (6.1%)	2 (6.1%)	1.000
Incisional residual myometrial thickness (milimeter, minumum-maximum)	0.53 (0.37-0.70)	0.57 (0.31-0.69)	0.207

Table 5 Evaluation of the women who had more than one cesarean section and comparison of these patients by the different closure techniques of the uterus

	More than one cesarean Single-layer locked continuous Group (n=33)	More than one cesarean Double layer un-locked continuous (n=33)	P value
Age (year)	30.06 ± 5.26	30.68 ± 5.23	0.611
Body Mass Index (kg/m²) (kg/m²)	27.88 ± 5.42	27.96 ± 4.41	0.939
Gravidity (n)	2 (2-7)	3 (2-4)	0.132
Previous cesarean numbers (n)	2 (2-4)	2 (1-4)	0.397
Birth weight (gram, minumum-maximum)	3309 ± 453.29	3267.24 ± 375.84	0.669
Smoking (n,%)	6 (17.1%)	9 (23.7%)	0.688
Post-menstrual bleeding (n,%)	2 (5.7%)	2 (5.3%)	1.000
Heavy menstrual bleeding (>7 days) (n,%)	2 (5.7%)	4 (10.5%)	0.676
Post-coital bleeding (n,%)	3 (8.6%)	1 (2.6%)	0.344
Dysmenorrhea (n,%)	4 (11.4%)	8 (21.1%)	0.428
Dyspareunia (n,%)	7 (20%)	8 (21.1%)	1.000
Wound site infection (n,%)	1 (2.9%)	2 (5.3%)	1.000
Numbers of the women detected isthmocele	4 (11.4%)	3 (7.9%)	0.703
Incisional residual myometrial thickness (milimeter, minumum-maximum)	0.42 (0.30-0.65)	0.51 (0.39-0.62)	<0.001

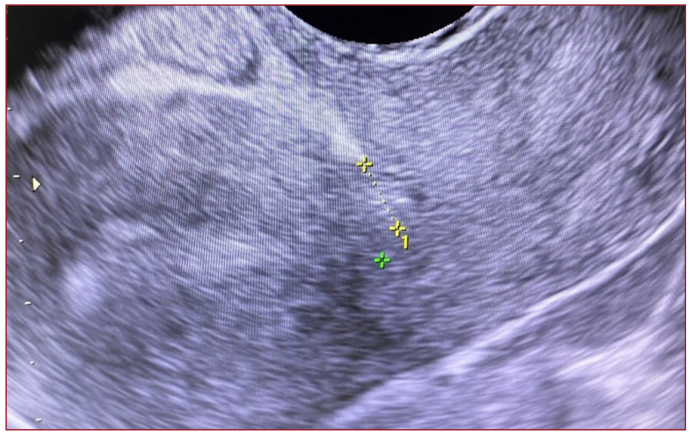

Figure 2. Transvaginal ultrasonographic view of the woman without isthmocele

Residual myometrial thickness

DISCUSSION

The cesarean section can be considered one of the most essential operations for the fetus and the patient. It provides a safe consequence for the baby, mother, and even for the obstetrician. Besides the serious complications that can occur even in a primary cesarean, that should be kept in mind that if it is not performed in the proper situations, the results could be more disastrous. The other biggest problem of the cesarean section is the possible risks during the consequent pregnancies especially the placental adherent syndromes. Isthmocele and the thin residual myometrial thickness are also consequences of the cesarean section. In this present study, the aim was to evaluate the effect of the cesarean section on these parameters. This was a unique study due to being the prospective randomized cohort trial. The limitation of the study was the small study population and the lack of long-term follow-up. The rate of the women who detected have isthmocele was 7.9%. This was a serious result due to the high cesarean rates worldwide. In a recent study, the rate of isthmocele was declared as 45.6%.[13] This is a remarkable result due to the possible risks. The cesarean scar defect is the major risk factor for placenta accreata spectrum (PAS) which is one of the most difficult condition to operate in obstetrics and gynecology. In a recent opinion, it was depicted that PAS is related to uterine dehiscence, not placental invasion!.[14] The lower segment of the uterus consisted of more fibrous tissue and less muscle fiber than the upper segment of the uterus. Some researchers have declared that the incision at the lower segment may cause an inadequate healing process which leads to scar defects thus the hysterotomy incision could be done at the upper limit of the uterine lower segment for better healing and to decrease the risk of inadequate uterine scar healing.[14,15] Besides the place of the hysterotomy during a cesarean, the patients' healing process is also the major step of the adequate consequences. In a recent study, it was declared that the healing process can continue up to six months or more,[16] therefore the women underwent ultrasonography in the 6th month after the operation, and all the ultrasonography examinations have been performed by the same physician in the present study.

The closure technique of the hysterotomy incision has been debated for years. Even the Cochrane Review exposed that the single-layer closure technique was related to faster operation time and less blood loss, however, a recent meta-analysis has remarked the inadequate powers of the studies.[17,18] In the present study, there was no statistically significant difference in terms of the abnormal menstrual bleeding, dysmenorrhea, dyspareunia, isthmocele occurrence, and the residual myometrial thickness comparing the single-layer locked continuous technique and double-layer un-locked continuous technique. In a contemporary study, the authors have investigated the uterine closure technique in the cesarean. They have performed transvaginal ultrasonography at the 6th week and the 24th month postoperatively and depicted that there was no statistical difference comparing the residual myometrial thickness and isthmocele occurrence. At the long-term follow-up, the double-layer closure group had higher residual myometrial thickness.[19] Our results were similar to that study.

The occurrence of isthmocele has been declared with a rate of 45% to 86% in several studies.[13,20] In the present study, the rate was 7.9%. The major reason for that difference might be the different considered thresholds for diagnosis. The increased cesarean rate was the major risk factor that can be easily estimated. The version of the uterus has been depicted as a risk factor, however, in the present study, anteversion and retroversion of the uterus did not differ statistically difference.[20] The single-layer closure of the uterus was also relieved as a risk factor for isthmocele in a systematic review.[20] The rates of isthmocele in the single layer and double layer uterine closure were 8,8 % and 7% respectively. The rate was higher in the single-layer group however comparison of the group did not differ statistically. That might be related to the few diagnosed cases of isthmocele. That result was also similar to a recent meta-analysis.[21]

As aforementioned, the comparison of uterine closure technique was not a nowel investing subject. However, there was lacking prospective randomized controlled studies. The purpose of that study was to fill that issue. As the limitation of the study, more women should be included in the study, and longer follow-up is necessary. As a summary of the literature; comparing the double versus single closure technique: No statistical difference was detected in terms of isthmocele incidence,[19,21] uterine dehiscence, and rupture,[21-23] thicker residual myometrium in double-layer technique,[19,21,22,24] less dysmenorrhea in double-layer closure.[22]

Overall comparison of single and double technique no difference in uterine rupture, however, the risk increased in locked single technique than double-layer closure,[23] less uterine rupture in the double-layer group.[25] The operative time was 3.9 minutes longer and niche prevalence was 4.7% higher after double-layer closure.[26] The double-layer

is associated with a thicker lower segment in the following pregnancy at the late third trimester of pregnancy.[27] Single-layer closure was associated with more bladder adhesion yet similar abdominal adhesion. However, no data has been exposed about the injury of the bladder.[28]

CONCLUSION

To sum up, the literature has exposed that endometrium should be included through the repair procedure. There was no strong evidence upon to support whether single layer closure or double layer closure technique. Women whose hysterotomy insicions were closed with double-layer un-locked continuous technique have a thicker resudial myometrium than single layer closure group despite the lack of significant difference in terms of isthmocele incidence, or menstrual disorders comparing the single layer versus double-layer closure. Although there was no significant difference in terms of isthmocele incidence, closure of the hysterotomy incision via double layer un-locked continunous technique in the women who underwent repeated cesarean section have thicker residual myometrium. Reviewing the literature might give us clues about decreasing using locked sutures while closing the incision. New data are needed to determine the appropriate place (the upper side of the lower segment) for hysterotomy in the cesarean section for secure and better healing.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Bursa Yuksek Ihtisas Training and Research Hospital Ethical Committee (Project Number: 2011-KAEK-25 2020/06-02).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Investigation of the Effect of Serum Leptin, Adiponectin, Resistin, C Peptide, IL-10, IL-22, and Visfatin Levels on Survival in Patients with Advanced Gastric and Colon Cancer

Serum Leptin, Adiponektin, Resistin, C Peptid, IL-10, IL-22 ve Visfatin Düzeylerinin İleri Evre Mide ve Kolon Kanserli Hastalarda Sağkalıma Etkisinin Araştırılması

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Abstract

Aim: Pathogenesis of cancer cachexia is not fully understood yet; however, adipocytokines are considered necessary in this context. We aimed to evaluate role of serum adiponectin, leptin, visfatin, resistin, C-peptide, IL-10 and IL-2 levels in the pathogenesis of cancer cachexia and to find out whether they are predictors of cachexia and to reveal their correlation with survival.

Material and Method: Fifty-three patients (34 males) and 20 healthy subjects as the control group were included in this study. Blood samples were stored in a deep freezer at -70°C and all samples were analyzed with an appropriate biochemistry kit. Along with demographic data and laboratory test results, serum adiponectin, leptin, IL-10, IL-22, C peptide, resistin, and visfatin levels were measured at 3 different times in both inpatient and control groups.

Results: There was no statistically significant relationship between adipocytokine levels and progression-free survival. Higher resistin and IL-10 levels were associated with shorter overall survival (p=0.035, p=0.14, respectively). There was no significant relationship between other cytokines and overall survival. Multivariate analysis has shown that higher serum Ca 19.9 levels (OR 0.226, P=0.005), lower BMI (OR 5.726, p= 0.007), higher serum IL-10 levels (OR 0.329, p= 0.042) were factors showing an impact on progression-free survival; lower serum albumin levels (OR 0.282, p=0.013), higher serum LDH levels (OR 0,338, p=0.012), low BMI at diagnosis (OR 5.19, p<0.0005) were factors having an impact on overall survival.

Conclusions: In our study, a correlation was found between resistin, adipocytokine, and IL-10 levels and overall survival.

Keywords: Cancer cachexia, adipocytokines, adiponectin, gastric cancer, colon cancer

Öz

Amaç: Kanser kaşeksisinin patogenezi henüz tam olarak anlaşılamamıştır; ancak adipositokinlerin bu bağlamda önemli olduğu düşünülmektedir. Serum adiponektin, leptin, visfatin, resistin, C-peptid, IL-10 ve IL-2 düzeylerinin kanser kaşeksisinin patogenezindeki rolünü değerlendirmeyi ve kaşeksinin belirleyicileri olup olmadıklarını ve sağkalım ile korelasyonlarını ortaya çıkarmayı amaçladık.

Gereç ve Yöntem: Elli üç hasta (34 erkek) ve kontrol grubu olarak 20 sağlıklı kişi bu çalışmaya dahil edildi. Kan örnekleri -70°C'de derin dondurucuda saklanmış ve tüm örnekler uygun biyokimya kiti ile analiz edilmiştir. Demografik veriler ve laboratuvar test sonuçları ile birlikte serum adiponektin, leptin, IL-10, IL-22, C peptid, resistin ve visfatin seviyeleri hem yatan hasta hem de kontrol grubunda 3 farklı zamanda ölçüldü.

Bulgular: Adipositokin düzeyleri ile progresyonsuz sağkalım arasında istatistiksel olarak anlamlı bir ilişki yoktu. Daha yüksek resistin ve IL-10 seviyeleri, daha kısa genel sağkalım ile ilişkilendirildi (sırasıyla p=0.035, p=0.14). Diğer sitokinler ile genel sağkalım arasında anlamlı bir ilişki yoktu. Çok değişkenli analiz, daha yüksek serum Ca 19.9 düzeylerinin (OR 0.226, P=0.005), daha düşük BMI (OR 5.726, p= 0.007), daha yüksek serum IL-10 düzeylerinin (OR 0.329, p= 0.042) progresyonsuz sağkalıma etki gösteren faktörler olduğunu göstermiştir. Daha düşük serum albümin seviyeleri (OR 0.282, p=0.013), daha yüksek serum LDH seviyeleri (OR 0.338, p=0.012), tanı anında düşük BMI (OR 5.19, P<0.0005) genel sağkalımı etkileyen faktörlerdi.

Sonuç: Çalışmamızda, resistin, adipositokin ve IL-10 düzeyi ile genel sağkalım arasında bir ilişki saptandı.

Anahtar Kelimeler: Kanser kaşeksisi, adipositokinler, adiponektin, mide kanseri, kolon kanseri

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INTRODUCTION

Cachexia is defined as a complex process including a multitude of factors such as adipose tissue loss due to lipolysis, loss of striated muscle, increase in energy expenditure during rest, and decrease in food intake.[1,2] Nowadays cachexia is used to define severe weight loss due to starvation or disease; however, it also points out a body mass index (BMI) < 18.5 kg/m^2. Recently, > 6% weight loss during the last 6 months along with hypercatabolic state during life-threatening conditions such as cancer are described as cachexia.[1-3] Cancer cachexia is a multifactorial syndrome occurring because of a lack of food intake in which various metabolic abnormalities, including hypermetabolism. There is an active catabolic process developing because of systemic inflammation involving multiple mediators including proinflammatory cytokines, neuroendocrine hormones, or factors inherent to the tumor itself.[4]

Cancer Cachexia is Evaluated Mainly in Two Groups

Primary cachexia: It is the result of metabolic alterations. Systemic inflammatory response is triggered and released biochemical substances (cytokines such as TNF-α, IL-1, IFN-γ, IL-6) increase metabolic rate and suppress appetite very early and lead to early satiety. As a result of metabolic abnormalities anorexia develops and loss of muscle and adipose mass ensues anorexia.[5] Based on data from some patients with cancer, it is suggested that there may be correlation between increased cytokine levels and progression of cancer.[6] Along with inflammatory process several biochemical hormones (visfatin, leptin, resistin) are released. As a result of this inflammatory process loss of adipose tissue and muscle mass occur.[7]

Secondary cachexia: Occurs because of factors impeding the intake of food. Mechanic obstruction due to tumor, taste, and odor abnormalities due to chemotherapy, diarrhea or constipation, fatigue, mucositis, nausea, vomiting, and pain are the most common accompanying symptoms and signs.[5] There is another term in the literature tertiary cachexia. It emerged after the detection of some findings that pointed out the impact of psychosocial factors on dietary intake in advanced-stage cancer patients.[7,8]

It's considered that the relationship between the tumor and the host contributes to the development of cachexia. Both experimental and clinical observations have revealed the presence of two types of catabolic factors. The first type is tumor-derived cachexia (proteolysis forming factor and lipid-mobilizing factor) and the other type is proinflammatory cytokines associated with the host (IL-1, IL-6, TNF- α, interferon-γ, cachexin, etc.). Furthermore, the imbalance between proinflammatory and anti-inflammatory cytokines is also suggested as a contributor to cachexia.[9] In recent years, importance of adipose tissue is emphasized in studies on cancer cachexia.[10]

Adiponectin, leptin, resistin is visfatin are among the adipokines exerting significant effects on lipid metabolism. Leptin suppresses food intake and stimulates energy consumption. Adiponectin and resistin are associated with body mass index and insulin resistance.[10] Visfatin stimulates angiogenesis by increasing endothelial proliferation. This was found to be associated with cancer development and cardiovascular diseases.[11] Higher concentrations of C-peptide are found to be directly related to cancer risk in some studies.[12,14] IL-10 is an anti-inflammatory cytokine and suppresses inflammatory process. In chronic gastritis excessive production of IL-10 allele may lead to helicobacter pylori colonization and mucosal inflammation.[15] IL-22 is a more recently described cytokine relative to others and it's suggested as a marker for GIS cancer screening and a target for treatment in the future.[16] Relationship between systemic inflammation and cancer and cachexia syndrome is not fully understood yet. However, now it's accepted that adipokines and proinflammatory cytokines have significant roles in these clinical pictures. One of the cancers leading to cachexia in the advanced stages is gastrointestinal system (GIS) cancer.[17] In this study, we aimed to evaluate role of serum adiponectin, leptin, visfatin, resistin, C-peptide, IL-10 and IL-22 levels in the pathogenesis of cancer cachexia and to find out whether they are predictors of cachexia and to reveal their correlation with survival.

MATERIAL AND METHOD

Pamukkale University Medical Faculty Medical Ethics Board approved our study with approval number 12.10.2010.06 and 53 consecutive chemotherapy-naive patients who have referred to our hospital and pathologically diagnosed as having gastric, colon, and rectum carcinoma were evaluated. The patients in advanced stages (stage III and IV) of the disease with ECOG performance status 0, 1, and 2 were included. The patients with performance status 3 or worse during the referral, patients in earlier stages of the disease, and who haven't signed written informed consent were excluded from the study. A control group consisting of 20 healthy individuals and not using any medication was established. The age and sex of the individuals in the control group were matching with the patient group. Weight loss during the time of diagnosis was described as weight loss >10% in the last 6 months ad cachexia was described as BMI ≤18.5. The individuals within both groups were interviewed about the object and scope of the study and written informed consent from patients was obtained.

Biochemical Analysis

From the advanced-stage gastrointestinal system (gastric and colorectal) cancer patients referring to Pamukkale University Medical Faculty Medical Oncology Department for treatment and from the control group consisting of healthy volunteers 15 ml venous blood samples were obtained to vacuumed plain tubes after at least 8-12 hours of overnight fasting at 08:00-09:00 hours before treatment and at 3rd and 6th months after treatment and the blood was centrifuged at 15000 rpm for 15 minutes to separate serum and it was stored at -70 °C in the deep freeze and the tests were done by using all of the samples with appropriate biochemical kits.

Measurements (Human adiponectin, leptin, IL-10, IL-22, C peptide, resistin, visfatin-Firm: Boster Immunoleader Ltd.) were done by ELISA (Enzyme-Linked Immunosorbent Assay) method (Digital and analog system, DAS, Plombara Sabina Italy). Adiponectin, leptin, visfatin, resistin, C-peptide IL-10, and IL-22 cut-of values were calculated. The values were 3.6258 ng/ml for Adiponectin, 2319,5459 pg/ml for leptin, 11.0442 pg/ml for resistin, 7350.5334 pg/ml for visfatin, 9.4532 ng/ml for C-peptide, 157,7016 pg/ml for IL-10, 116.1121 pg/ml for IL-22. Values equal to or lower than these figures were considered low and higher levels were considered high. Demographic characteristics of patients, type of tumor, and previous chemotherapies were recorded by using data from the patient charts. From the obtained blood samples hemogram was performed by using CELL-DYN 3700 Systems and CELL-DYN Sapphire instrument and albumin, CRP, Lactate dehydrogenase (LDH), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (AST), glucose was measured by Roche/Hitachi Cobas c Systems, Cobas c 501 and Roche/Hitachi Cobas c Systems, e 601 Module instrument.

Anthropometric Measurements

Height, weight, waist and hip circumference, arm circumference, and triceps thickness of the patients and control group were measured before treatment and at the time of referral. Height and weight measurements were done on a calibrated scale with a height gauge by the same person while the subjects were in a fasting condition. Body mass index (BMI) was calculated by this formula: weight (kg)/height^2(m^2). 18.5-24.9 kg/m^2 was considered normal and >25 kg/m^2 was considered overweight and obese.[18] For waist circumference measurements benchmarks were the narrowest diameter between arcus costarium and spina iliaca anterior posterior (superior); for hip circumference the highest diameter traversing gluteus maxiumus in the back and symphysis pubis at the front and the measurement was done by a tape measure. Waist/hip ratio was calculated (normal values were < 0.95 for males and < 0.8 for females).[18] Arm circumference was measured from the midpoint of the distance between olecranon and acromion. <18 cm and <20 cm was considered pathological respectively for females and males.[19] Triceps thickness was measured to evaluate thickness of subcutaneous adipose tissue and the measurement was done by using a caliper which is a special device from the midpoint of the distance between olecranon and acromion 3 times and average of these measurements was recorded. Values <10 mm and <13 mm were considered as lack of nutrition respectively for males and females.[19]

Statistical Analysis

Social Sciences version 22. 0 (SPSS-22.0, for windows) package program was used for statistical analysis. Descriptive statistics were as percentage for categorized variables and as mean for continuous variables. In dual comparisons Ki-square test was used for categorized variables and for continuous variables non-parametric tests Mann Whitney-U or Kruskal-Wallis were used because the distribution was non-normal and Freidman test was used in case there is repeated analysis. In dual comparisons of survival analysis Kaplan Meier method was used and statistical differences were evaluated by log rank test. The highest sensitivity and specificity values of cut-off values were selected by using SPSS 22.00 version roc-curve analysis.

RESULTS

A total of 53 (34 male, 64.2%) patients with advanced stage grade (III and IV) colorectal or gastric cancer were included. Main clinical and demographic characteristics are shown in **Table 1**. 16 males (80%) and 4 females (20%) were selected as a control group. The mean age was 63.1±6.3 years. They had no comorbidities, and their performance was good (ECOG PS 0). In the control group cachexia, anemia, leukocytosis, high CRP or LDH level and low albumin level haven't been observed and in fifteen subjects (75%) BMI was > 25 kg/m^2 and none of them had a history of tobacco or alcohol use.

Table 1 Demographic and clinical characteristics of the patients (before treatment)

Characteristics	Median-year, (range)
Age	63.32 (39 -79)
Characteristics	n(%)
Gender	
Male	19 (35.8)
Female	34 (64.2)
Organ involvement	
Stomach	25 (47.16)
Colon	25 (47.16)
Rectum	3 (5.66)
Stage	
III (three)	21 (39.62%)
IV (for)	32 (60.37%)
Tobacco use (yes/no)	28/25 (52.8/ 47.2)
Use of Alcohol	46/7(86.8/ 13.2)
Performance status(0/1) 2	44 (83) /9 (17)
Comordity (yes/no)	25/28 (47.2/ 52.8)
Weigt loss during (yes/no)	48/5(90.6/ 9.4)
Family history of cancer (yes/no)	11/42 (11.32/ 88.68)

*p < 0.05 is considered as significant. SD: standart deviation

Age, gender, anthropometric measurements, biochemical test values, serum adiponectin, leptin, resistin, visfatin, C peptide, and IL-22 values were compared between groups (**Table 2**). As it's shown in **Table 2** resistin levels were higher in the patient cohort compared to the control group and the increase was statistically significant (p<0.001). Adiponectin and visfatin levels were lower in the patient cohort and the difference was statistically significant for both parameters (p=0.002, p=0.001). There was no statistically significant difference between the groups in terms of Leptin, C-peptide, IL-10, and IL-22 values. In **Table 3** prospective cachexia-associated biomarker follow-up results of the patient group were measured at 3 different times. There was no statistically significant difference in the prospective cachexia-associated biomarker follow up results of patient group measured in 3 different time except serum C-peptide value (p=0.002).

Table 2 Characteristics of patient and control group (mean±SD).

	Patient	Control	P
Age (year)	63.3±10.4	63.1±6.2	0.484
Sex (female/male)	19(35.8)/34(64.2)	4(20)/16(80)	0.263
Height(cm)	162.84±8.95	171.1±6.75	0.001*
Weight (kg)	64.58±12.27	80.6±10.8	<0.001*
BMI (kg/m^2)	26.49±3.66	27.2±2.9	0.002*
Waist circumference (cm)	86.28±14.38	98.2±7.6	0.001*
Hip circumference (cm)	93.96±14.87	104.2±5.4	<0.001*
Triceps thickness (mm)	1.79±0.62	3.6±0.5	<0.001*
Arm circumference (cm)	23.6±4.92	32.2±2.2	<0.001*
Hemoglobin (gr/dl)	12.53±1.89	14.5±1.0	<0.001*
WBC (K/µL)	8632±3523.6	7503.5±335.7	0.407
Neutrophils (K/µL)	5888.8±2899.3	4112.5±272.7	0.009*
PLT (K/µL)	314018.8±1.19	249050±8938.2	0.011*
Albumin (g/dl)	3.73±0.72	4.4±0.3	<0.001*
CRP (mg/dl)	3.53±5.22	0.3±0.1	<0.001*
Glucose (mg/dl)	116.53±45.55	95.0±4.9	0.021*
LDH (U/L)	374.96±708.02	194.1±7.1	0.209
IL-10 (ng/ml)	202.89±148.27	201.46±230.42	0.350
IL-22 (ng/ml)	185.89±153.62	215.83±96.04	0.070
C peptid (ng/ml)	8.23±2.02	8.66±1.58	0.496
Adiponectin (ng/ml)	5.18±3.89	8.01±3.87	0.002*
Leptin (ng/ml)	2.254±4460	2.39±3.7	0.990
Resistin (ng/ml)	7365.39±215.77	7125.06±352.91	<0.001*
Visfatin (ng/ml)	12.18±28.22	16.88±17.52	0.001*

*p < 0.05 is considered as significant. SD: standart deviation
**BMI: body mass index; WBC: White Blood Cell, PLT: platelets; CRP: c-reactive protein; LDH: Lactate dehydrogenase

During the median 8 months of follow-up (range 6-21 months) the disease has progressed in 16 of the 53 patients (30.18%). Progression-free survival was assessed and there was no statistically significant difference between those with high and low levels of leptin, adiponectin, resistin, C peptide, IL-22, and visfatin (p=0.711, p=0.568, p=0.774, p=0.997, p=0.405, 0.390, respectively) regarding progression. In patients with higher IL-10 levels progression-free survival was 36.64 weeks and in those with lower levels, it was 52.88 weeks (p=0.023). As it's shown in **Table 4** after Cox regression analysis 3 of the 5 parameters within the model were found to be statistically higher.

Table 4. Multivariate analysis results of progression free survival

Multivariate analysis results of progression free survival */**			
	OR	95%CI max-min	P
CA-19-9	0.226	0.080-0.639	0.005**
BMI	5.726	1.598-20.514	0.007**
IL-10	0.329	0.110-0.960	0.042**
Pathology			
Adenocarsinoma	0.389	0.035-4.375	0.614
Signet ring cell	0.798	0.049-13.091	0.953
Undifferentiated	4.599	0.171-123.909	0.144
Hemoglobin	0.276	8.6-13.2	0.20

Cox regression analysis was done and 5 parameters were evaluated in the model and 3 parameters was found to be significant.**p < 0.05 is considred significant. SD: standart deviation, OR:odds ratio BMI: body mass index

In patients with high levels of leptin, adiponectin, C peptide, IL-22, and visfatin mean overall survival wasn't significantly different from those with low levels (p=0.787, p=0.702, p=0.224, p=0.954, p=0.205). As it's shown in **Figure 1**, the mean overall survival was 9 months in patients with a high level of IL-10 and 14 months in patients with low levels of IL-10. The difference was statistically significant (p=0.014). As it's shown in **Figure 2**, the mean overall survival was 9 months in patients with a high level of resistin and 14 months in patients with a low level of resistin. The difference was statistically significant (p=0.035). In Cox regression analysis, hypoalbuminemia, high LDH level, and presence of low BMI at the time of diagnosis caused statistically significant overall survival differences (**Table 5** and **6**).

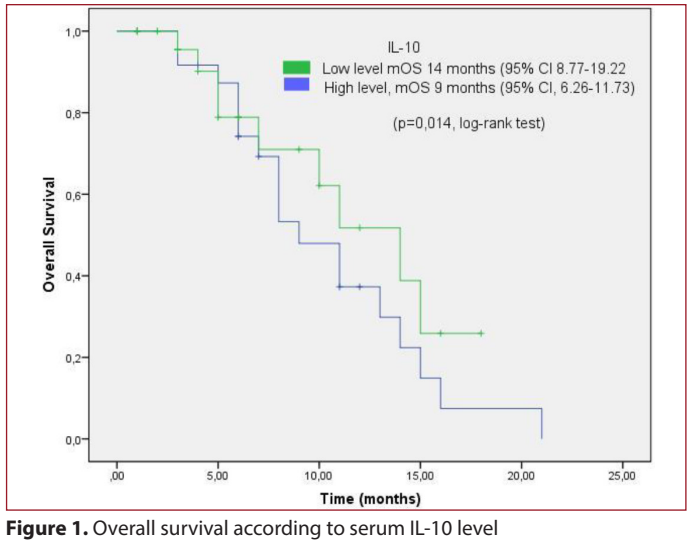

Figure 1. Overall survival according to serum IL-10 level

Table 3 Prospective cachexia-associated biomarkers follow up results of patient group measured in 3 different time period (mean±SD).

(ng/ml)	Before treatment		3rd month		6th month		P
	n	mean±SD	n	mean±SD	n	mean±SD	
IL-10	54	202.89±148.27	37	202.5±172.88	14	204.58±250.02	0.526
IL-22	54	185.89±153.62	37	130.68±345.56	14	208.18±530.69	0.238
C peptide	54	8.23±2.02	37	10.8±0.95	14	9.09±1.93	0.002*
Adiponectin	54	5.18±3.89	37	2.50±1.57	14	4.1±3.02	0.135
Leptin	54	2.254±4460	37	1812.3±694.9	14	1976.1±519.8	0.138
Resistin	54	7365.39±215.77	37	7249.6±443.3	14	7200.2±377.1	0.751
Visfatin	54	12.18±28.22	37	21.6±42.87	14	18.96±27.12	0.424

*p < 0.05 is considered as significant. SD: standart deviation

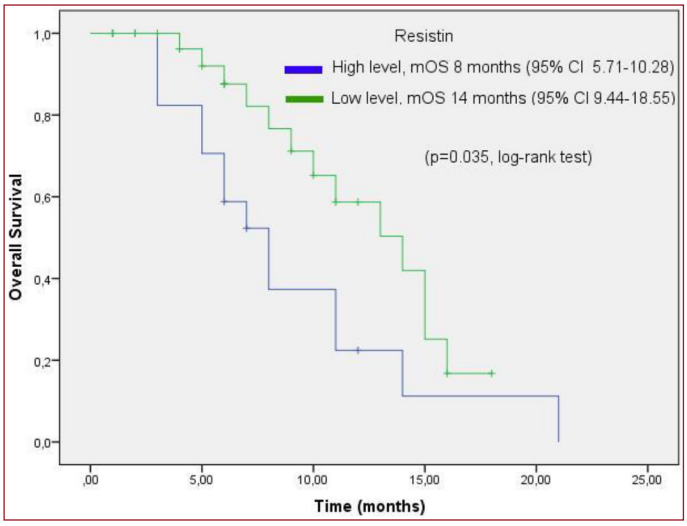

Figure 2. Overall survival according to serum resistin level

Table 5. Multivariate analysis results in overall survival -1

Multivariate analysis results of overall survival -1 */**			
Variable	**OR**	**95%CI max-min**	**P**
Hypoalbuminemia	0.282	0.104-0.764	0.013**
LDH	0.338	0.146-0.786	0.012**
Anemia	0.470	0.200-1.102	0.083
CRP	0.676	0.116-3.949	0.664
Leucocytosis	0.736	0.325-1.666	0.462
CEA	0.944	0.360-2.475	0.906

* Overall survival multivariate analysis performed by Cox regression analysis and 6 parameters were evaluated in the model and 2 parameters was found to be significant.**p < 0.05 is considred significant. SD: standart deviation
** CRP: c-reactive protein; LDH: Lactate dehydrogenase

Table 6. Multivariate analysis results of overall survival-2

Multivariate analyssi results in overall -2*/**			
Variable	**OR**	**9 5%CI max-min**	**P**
BMI during diagnosis	5.19	2.093-12.867	<0.005**
LDH	0.257	0.087-0.761	0.014**
IL-10	0.585	0.233-1.470	0.254

* Overall survival multivariate analysis performed by Cox regression analysis and 3 parameters were evaluated in the model and 2 parameters was found to be significant. **p < 0.05 is considred significant. SD: standart deviation

DISCUSSION

Gastrointestinal system cancers are the third leading cause of cancer deaths after lung cancer in males and lung and breast cancer in females.[20] Prevalence of malnutrition in gastrointestinal system cancer patients is 42-87%.[21-23] In cancer patients, weight loss was found to be correlated with lower survival and decrease in life quality.[24,25] Patients with weight loss comprised 90.5 % of our patient cohort. In anthropometric measurements, height, weight, BMI, waist circumference, hip circumference, triceps thickness, arm circumference was lower in patient's cohort compared to control group and the difference was statistically significant. Moreover, in the patients with weight loss at the time of diagnosis waist circumference, hip circumference, weight, BMI were lower. In our study, it was observed that weight loss at the time of diagnosis had an impact on progression and survival.

In the subcutaneous adipose tissue leptin production is more than in visceral adipose tissue and has the best positive correlation with body mass index and body fat ratio.[26] In a study regarding leptin levels and including 39 patient's leptin level was found to be statistically significantly lower in cachectic GIS cancer patients and low level of leptin was found to be associated both with loss of adipose cells and increase in inflammatory cytokines.[26] Levels were low in gastrointestinal and pancreatic cancer patients, but high in breast and gynecological cancers.[27,28] It was reported that there is a tendency for lower survival in patients with weight loss and poor performance though there was no correlation between these parameters and time to progression of the disease.[29] In our study prospective leptin follow up results of patient group measured in 3 different time period revealed no significant finding (p=0.138). In a study by Nakajima et al.[30] leptin levels of gastric cancer patients and healthy controls were compared. According to the results of this study leptin levels progressively decreased as the stage of the disease progressed.[30] In our study, the mean progression-free survival was 46. 05 weeks in patients with high levels of leptin and 46.18 weeks in patients with low levels of leptin (p=0.711). Mean overall survival was 44.76 weeks in patients with high levels of leptin and 43.81 weeks in patients with low levels of leptin; however, the difference wasn't statistically significant. Adiponectin is a protein released from adipose tissue. The physiological role of adiponectin is not fully elucidated yet; however, there are some studies pointing out its antiatherogenic and anti-inflammatory effects on endothelial cells and macrophages and showing a decrease in adiponectin levels in the presence of hypertension, diabetes, and metabolic syndrome.[31,32] In a study carried out on breast and colon cancer patients; advanced age and female sex were found to be correlated with high adiponectin levels.[33] Adiponectin blocks the effects of TNF-α. Lower adiponectin level increases the effect of TNF-α on tumor cell proliferation and thus promotes carcinogenesis. In our study, in the adiponectin patient group adiponectin was lower compared to the control group. Proinflammatory and growth-stimulating effects of adiponectin on colonic epithelial cancer cells were detected. In a prospective study, plasma adiponectin level was conversely related to colorectal cancer risk in males. This correlation was found to be independent of BMI; waist circumference, waist: hip ratio, and physical activity.

It has been suggested that resistin is a mediator of metabolism including particularly glucose metabolism, a regulator in adipogenesis and a modulator in inflammation.[35] In a study conducted on 30 health volunteers and 60 gastric cancer patients there was no direct relationship between resistin level and cancer cachexia. Effects of resistin in cancer cachexia are due to insulin resistance and ineffective use of blood glucose. Resistin level was found to be higher in cachectic patients relative to non-cachectic patients and healthy volunteers.[36] In our study, resistin was higher in the patient group compared

to the control group (p<0.001). Moreover, it was found that resistin levels were higher in patients with weight loss at the time of diagnosis but there was no difference in patients and control group subjects without weight loss. Higher resistin levels in patients with weight loss at the time of diagnosis support the notion that resistin may be involved in this hypercatabolic process. In a case-control study conducted on colorectal cancer patients, Nakajima et al. stated that resistin and visfatin each may be a good biomarker in predicting potential colorectal malignancy and stage progression in colorectal cancer independent from BMI.[37] Overall survival was worse in patients with high resistin level compared to patients with low resistin level. The difference was statistically significant (8 months vs 14 months, p=0.035). Our study has shown that resistin is involved in cancer and cachexia as a proinflammatory cytokine and although it can't be used as a diagnostic or prognostic marker yet there is still a need for further studies on this substance.

C peptide is secreted in equal amounts with insulin after insulin biosynthesis and thus may be used as an endogenous insulin secretion marker; however, its cellular effects aren't fully elucidated, yet.[30] It's known that components of metabolic syndrome increase cancer risk. In our study, C peptide levels were higher in the control group compared to patient group, but the difference wasn't statistically significant. In the group with weight loss C peptide level was higher but difference wasn't statistically significant (p=0.260). In a study by Nakajima et al.[30] C peptide levels of gastric cancer patients were compared with healthy controls. There was no correlation between BMI and C-peptide level. According to the results of the same study, in parallel to progression of the disease stage BMI and C peptide levels have progressively decreased.[30] On the other hand, in our study, C Peptide level was 8.23ng/dl in the 1st measurement, 10.8 ng/dl in the 2nd measurement and 9.09 ng/dl in the 3rd measurement. Serum C peptide level which was lower than cut off value at the time of diagnosis was found to be higher than cut off value in the 2nd and 3rd measurements. The difference was statistically significant (p=0.002). In patients with higher C peptide level median progression free and overall survival was longer but the difference wasn't significant (p=0.097, p= 0.224). Intracellular signaling pathways of C peptide is not fully known and cellular mechanism links are clinically important for components of metabolic syndrome and carcinogenesis. We assume that furthermore comprehensive studies about C peptide and gastrointestinal cancers are needed.

Even though cancer cachexia couldn't have been fully elucidated, currently some important key mediators are discovered. IL-1, IL-6, IL-10, TNF-α, IFN-g are the mediators with a proven role in cancer cachexia pathogenesis.[38] It's assumed that IL-10 induces increase in cell proliferation, and this leads to decrease in apoptosis and thus promotes tumor growth. IL-10 production and release are conducted by immune cells along with cancer cells. Shibata et al. have studied serum IL-10 and IL-12 levels in colorectal cancer patients. IL-10 levels were higher in cachectic patients compared to healthy control group. In the same study, IL- 10 levels were lower in early-stage colorectal cancer.[39] In a study by Stanilov et al.[40] increasing IL-10 levels were reported to be related with progression in colorectal carcinoma. De Vita et al.[41] compared IL-10 levels measured before and after chemotherapy in advanced stage gastrointestinal system cancer patients. The levels were lower in those responding to chemotherapy than nonresponding patients. This study led to the premise that IL-10 levels measured before treatment may be helpful in detecting the disease regardless from progression. In the same study, IL-10 levels were higher in the carcinoma patients compared to control group.[41] Similarly, also in our study IL-10 level was higher in stage 4 diseases compared to stage 3; however, there was no statistically significant result between patient group and the control group (p=0.350).

In carcinogenesis role of immune response of the host, cytokines, immune mediators, and associated inflammation have been increasingly proven. IL-22 is a member of IL-10 and derived from T cells and it's responsible from epithelial immunity and mucosa tissue repair.[42] Thomson et al.[16] reported that IL-22 gene variation (rs1179251 SNP) is related with risk of colon cancer. In our study IL-22 level was lower in the patient group compared to control group (p=0.07). Furthermore, mean progression free survival was 45.64 weeks in patients with high IL-22 levels and 41.84 weeks in those with low levels and mean overall survival was 45.58 weeks in patients with high IL-22 levels and 46.06 weeks in those with low levels; however, differences weren't statistically significant (p= 0.405, p= 0.954).

Visfatin which is also known as Pre-B cell colony-enhancing factor (PBEF) is a recently described novel adipokine secreted from visceral adipose tissue.[43] It's biological function and its role within the mechanism as a cytokine couldn't be fully elucidated yet. It's presumed that by inhibiting visfatin activity treating cancer or an increase in sensitivity to chemotherapy may be possible.[43] In acute and chronic inflammation serum visfatin levels increased. During inflammation process its production increases and this leads to an increase in secretion of cytokines such as tumor necrosis factor -α (TNF-α), IL–1, IL–6, IL–10.[44] Nakajima et al.[30] reported that visfatin within the serum obtained from patients with colorectal or gastric cancers may be related with the stage and progression of the disease. Additionally, they suggested that visfatin may be a very good biological marker for potential malignancy and progression in colorectal adenocarcinoma. In our study we did noy detect any effect of visfatin levels on progression and mean progression free survival. Overall survivals were longer in patients with high visfatin levels compared to those with low levels, however, the results weren't significant (p=0.39, p=0.205). Detection of visfatin also in inflammatory cells and elevation in plasma levels during various inflammatory diseases implies that different cytokines may be effective in visfatin synthesis and secretion.

CONCLUSION

In this study, 53 advanced stage gastrointestinal system cancer patients and 20 healthy control group subjects were evaluated regarding their clinical and laboratory data. In the patient group BMI, weight, waist circumference, hip circumference, arm circumference, triceps thickness, hemoglobin, albumin, adiponectin, visfatin leptin, C-peptide and IL-22 levels were low; neutrophils, platelets, CRP, glucose, resistin WBC, LDH and IL-10 levels were high. Furthermore, a relationship between resistin which is a type of adipokine, and IL-10 level were detected. Our results were broadly in line with the literature. There is scarce amount of study in the literature about this issue. In our study, relatively low number of the patient cohort may prevent data which are statistically more significant to be obtained. We assume that, for a final decision accumulation of more literature is needed and studies with higher number of patients should be conducted.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethical Committee of Pamukkale University, Scientific Research Projects Commision dated 07/03/2013 and numbered 01, numbered 2011TPF009.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Predicting of Bacteremia in Patients with Acute Brucellosis Using Machine Learning Methods

Akut Brusellozlu Hastalarda Bakteriyeminin Makine Öğrenmesi Yöntemleri Kullanılarak Tahmin Edilmesi

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Abstract

Aim: Accurate and early diagnosis of brucellosis is crucial to slow the spread of the disease and provide rapid treatment to patients. The aim of this study was to develop a machine learning-based predictive model for the diagnosis of bacteremia in brucellosis patients based on some hematological and biochemical markers without the need for blood culture and bone marrow culture and to investigate the importance of this method in predicting bacteremia in brucellosis.

Material and Method: In this study, 162 patients over 18 years of age diagnosed with brucellosis were included and the patients were divided into two groups according to bacteremia status. Data were collected retrospectively and analyzed by machine learning. Twenty demographic, hematological, and biochemical laboratory parameters and 30 classifiers were used to predict bacteremia in brucellosis. The classifiers were developed using Python programming language. To assess the classification performance of the methods used, Accuracy (ACC), f-measure (F), and ROC under area (AROC) criteria were utilized. All classification methods were executed with a 15-fold cross-validation test set selection method. The feature importance method was used to select the most discriminative features for the classification of blood culture positivity.

Results: Extratree classifier with "entropy" criterion (ETC1) showed the best predictive performance with ACC values ranging between 0.5 and 1.00, F values between 0.53 and 1, and AROC values between 0.62 and 1. The neutrophil percentage, the lymphocyte percentage, the eosinophil percentage, alanine aminotransferase, and C-reactive protein values were determined as the most distinguishing features with scores of 0.723, 1.000, 0.920, 0.869, and 0.769, respectively.

Conclusion: This study showed that the ETC1 classifier may be helpful in determining bacteremia in brucellosis patients, and that elevated lymphocytes, alanine aminotransferase and C-reactive protein and low neutrophils and eosinophils may indicate bacteremic brucellosis.

Keywords: Brucellosis, brucella, machine learning methods, classification, bacteremia

Öz

Amaç: Brusellozun doğru ve erken teşhisi, hastalığın yayılımını yavaşlatmak ve hastalara hızlı tedavi sağlamak için çok önemlidir. Bu çalışmanın amacı, bruselloz hastalarında bakteriyemi tanısı için kan kültürü ve kemik iliğine kültürüne ihtiyaç duymadan bazı hematolojik ve biyokimyasal belirteçlere dayalı makina öğrenmesi temelli bir prediktif model geliştirmek ve bu yöntemin brusellozda bakteriyemiyi öngörmedeki önemini araştırmaktı.

Gereç ve Yöntem: Bu çalışmaya bruselloz tanısı konulan 18 yaş üstü 162 hasta dahil edilmiş olup, hastalar bakteriyemi durumuna göre iki gruba ayrıldı. Hastaların verileri retrospektif olarak toplandı ve makine öğrenmesi yöntemiyle analiz edildi. Brusellozda bakteriyemiyi tahmin etmek için yirmi demografik, hematolojik ve biyokimyasal laboratuvar parametresi ve 30 sınıflandırıcı kullanıldı. Sınıflandırıcılar Python programlama dili kullanılarak geliştirildi. Kullanılan yöntemlerin sınıflandırma performansını değerlendirmek için Doğruluk (ACC), f-ölçütü (F) ve alan altında ROC (AROC) ölçütleri kullanıldı. Tüm sınıflandırma yöntemleri 15 kat çapraz doğrulama test seti seçim yöntemi ile gerçekleştirildi. Kan kültürü pozitifliğinin sınıflandırılmasında en ayırt edici özelliklerin seçilmesi için özellik önemi yöntemi kullanıldı.

Bulgular: "Entropi" ölçütlü ekstratree sınıflandırıcı (ETC1), 0,5 ile 1,00 arasında değişen Acc değerleri, 0,53 ile 1 arasında değişen F değerleri ve 0,62 ile 1 arasında değişen AROC değerleri ile en iyi tahmin performansını gösterdi. Nötrofil yüzdesi, lenfosit yüzdesi, eozinofil yüzdesi, alanin aminotransferaz ve C-reaktif protein değerleri sırasıyla 0,723, 1,000, 0,920, 0,869 ve 0,769 skorlarıyla en ayırt edici özellikler olarak belirlendi.

Sonuç: Bu çalışma, ETC1 sınıflandırıcısının bruselloz hastalarında bakteriyemiyi belirlemede yardımcı olabileceğini, lenfosit, alanin aminotransferaz ve C-reaktif protein yüksekliğinin; nötrofil ve eozinofil düşüklüğünün bakteremik brusellozu gösterebileceğini göstermiştir.

Anahtar Kelimeler: Bruselloz, brusella, makine öğrenme yöntemleri, sınıflandırma, bakteriyemi

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INTRODUCTION

Brucellosis is a globally common zoonotic disease caused by Brucella spp. a Gram-negative intracellular bacterium. [1] It is endemic in many countries in Northern and Eastern Africa, Central Asia, India, Central and South America, and Mediterranean countries in Europe and the Middle East. [2] According to the World Health Organization (WHO), approximately 500,000 new brucellosis cases are reported annually. However, the true number of cases is higher than the reported number of cases.[3] Transmission of brucellosis is mostly due to the consumption of unpasteurized milk/dairy products in endemic countries and occupational exposure in developed countries.[4]

Symptoms and signs such as fever, sweating, fatigue, and osteoarthritis are frequently seen in brucellosis, and more serious conditions may occur in different organs.[4-6] Because the clinical presentation of brucellosis is variable and non-specific, confirmation of the diagnosis with laboratory tests is essential for providing appropriate treatment to the patient. Diagnosis of human brucellosis requires laboratory tests involving nucleic-acid amplification assays, serology, and culture. Bone marrow and blood culture are the gold-standard diagnostic tests.[3] The rate of blood culture positivity (bacteremia) in brucellosis varies between 15-90%. Especially in acute brucellosis, culture positivity rates are usually higher. [7] However, the results of these tests are delayed. The aim of this study is to predict bacteremia in acute brucellosis based on some hematological and biochemical markers of brucellosis patients without the need for blood culture and bone marrow culture. For this purpose, classification methods, one of the machine learning methods, were used in this study.

MATERIALS AND METHOD

The organization of this study is as follows:

Data Collection

Data were collected retrospectively in this study and 162 patients with a diagnosis of brucellosis were included in the study.

Patients over the age of 18 who were diagnosed with acute brucellosis and admitted to the Infectious Diseases and Clinical Microbiology outpatient clinic of Harran University Hospital between 2018 and 2020 were included in the study.

Hematologic and biochemical laboratory results and age/gender information of these patients were obtained from the hospital information management system.

Brucellosis definition: The criteria used for the diagnosis of brucellosis are growth in the culture of Brucella spp. in blood or other body fluids and together with clinical symptoms such as fever, sweating, chills, joint-muscle pain, headache, and weakness, being of serum Brucella tube agglutination titer equal to or greater than 1/160 or being of at least a four-fold titer increase in the serum sample taken at two-week intervals. The presence of clinical symptoms and signs for less than 2 months was considered acute brucellosis.[4]

Hematological and biochemical parameters: From the hematological examinations of the patients included in the study at the time of application; white blood cell (WBC), hemoglobin (HGB), hematocrit (HCT), platelet (PLT), neutrophil (NEUT), neutrophil % (NEUT%), lymphocyte (LYMP), lymphocyte % (LYMP%), monocytes % (MO%), eosinophil % (EOZ%), from biochemical tests; creatinine (CRE), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T.BIL), direct bilirubin (D.BIL), lactate dehydrogenase (LDH), FER, C reactive protein (CRP) results were evaluated.

Ethics Considerations

This study was supported by the Clinical Research Ethics Committee of Harran University with the number 22.10.21 on May 23, 2021. All procedures in the study were performed in accordance with the World Medical Association Declaration of Helsinki.

Data Preprocessing

Missing values were completed by using KNNImputer.[8] which is one of the Scikit-learn classes. KNNImputer is based on finding k neighbors nearest to the instance involving the missing values by using a distance measure (generally Euclidian distance). The missing values are completed by taking the arithmetic means of the relating values of the k-nearest neighbor.

Statistical Analyses

Statistical analysis was performed by using SPSS 21 package program (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Continuous variables were presented as mean ±standard deviation. Categorical variables were shown as frequencies and percentages. The normality of continuous variables was tested by using the One-Sample Kolmogorov-Smirnov test. Two independent samples t-test was utilized for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables to test whether the difference between the parameters of bacteremic and non-bacteremic patients was statistically significant. the p-value is lower than 0.05 and was considered statistically significant in all statistical tests.

Classification

In this study, classification which is one of the popular machine learning methods was used to predict the relationship between hematological and biochemical features and bacteremia. Classification is a process of predicting a function (f) between the features (X) and the labels (C) as f:X→C in the labeled data set.[9] The main objective of the classification is to assign the instances to a predefined class according to the features. Classification is performed in two main steps training and testing. In the training step, a classifier or

function (f) is predicted based on the relationship between the features (X) and the classes (C). The test step is to evaluate the classification performance of the predicted classifier by using various evaluation criteria. The original data set firstly is divided into two distinct subsets as training and test sets. There exist various test set selection techniques, especially Holdout and cross-validation. To determine the classification method, and provide the best prediction results, this study uses a cross-validation test set selection technique.[10]

Classification methods can be divided into two main categories as base and ensemble classifiers. The base classifier is based on predicting a single classifier for the classification problem. In this study, K-Nearest Neighbor (KNN), three Support Vector Machines (SVM) classifiers, Gaussian Naïve Bayes (GNB), Decision Tree Classifier (DTC), and Logistic Regression (LR) were used from the base classifier category. Ensemble classification methods are based on combining several base classifiers such as KNN, SVM, Bayes, etc. to improve the prediction performance. These methods can be divided into three main categories as bagging, boosting, and stacking.[11-14]

KNN classifier is based on finding the k nearest instances to new instance to be classified by using a distance function. For this objective, the distances of new instance to all instances in the data set are calculated. The distances are sorted as ascending and k instances nearest to new instance are found. The class of new instance is predicted by majority vote method.

SVM classifier is based on finding optimal hyperplane which maximizes the margin between the different classes. For the binary class and linearly separable classification problems, the process of SVM can be briefly described as follows. Let (x_i, y_i) be the training data set, where x_i is the ith input, consisting of p features and $y_i \epsilon \{-1, +1\}$ is the class label corresponding to of ith input. The separating line(for binary class problems) to be found can be written as follows:

$$w^T x + b = 0$$

Where w indicates the normal of the line and b is the bias. Support vectors are utilized to find the parameter of the line.

The SVM tries to find the hyperplane, which makes the margin ($\frac{2}{\|w\|}$) maximum. This problem is equivalent with the following optimization problem:

$$MinJ(w, b, \lambda) = \frac{1}{2\|w\|^2} - \sum_{j=1}^{k} \lambda_j [y_j(wx + b) - 1] \quad (2)$$

If the first derivative of the objective function given in Eq. (2) is taken separately with respect to w and b and set to 0, required equations for finding w and b are obtained. For two-class classification problems that are not linearly separable, the feature space is first transformed into a linearly separable space using a kernel function. Then, the objective function given in Eq. (2) is tried to be minimized.

Bayes Classification: Bayes classification is based on estimating probability of belonging of a new instance to given a class by using following equation:

$$P(C_j|\boldsymbol{X}) = \frac{P(\boldsymbol{X}|C_j) * P(C_j)}{P(\boldsymbol{X})} \; j = 1,2, \ldots, c \quad (3)$$

Where c is the number of class, $P(C_j)$ is the probability of class C_j, $P(\boldsymbol{X}|C_j)$ is the conditional probability that the instance is X, given that the class is C_j and lastly $P(C_j|\boldsymbol{X})$ is the conditional probability that the class is C_j, given that the instance is X. The instance, X, is assigned to the class with the highest probability of $P(C_j|\boldsymbol{X})$.

Logistic Regression: Similar to the Bayesian classification method, logistic regression estimates the probabilities of classes for a given X instance. For the binary outcome classification problems (such as the presence or absence of a disease), the probability is estimated as follows:

$$P(Y = 1|\boldsymbol{X}) = \frac{e^{(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p)}}{1 + e^{(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p)}} \quad (4)$$

Where, $P(Y = 1)$ is the probability of presence of interested outcome, such as a disease. The probability of absence of interested outcome is estimated by using following equation:

$$P(Y = 0) = 1 - P(Y = 1) \quad (5)$$

In fact, logistic regression estimates the model parameters ($\boldsymbol{\beta}$) given in Eq. (4). For this objective, Eq. (5) is modified as follows:

$$\log\left(\frac{P(Y = 1|\boldsymbol{X})}{1 - P(Y = 1|\boldsymbol{X})}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p \quad (6)$$

Decision Trees (DT): DT is based on partitioning of the feature space into homogenous subsets, recursively. As a result of DT classification process, a tree-like structure consisting of a root node, multiple internal nodes, terminal nodes and branches is obtained. The root and internal nodes correspond to a feature in the data set. The terminal nodes include class labels. To construct the tree structure, some evaluation criteria such as information entropy, gain ratio and Gini index are used (Ahybridensemblemethodforpulsarcandidateclassification--AstrophysicsandSpaceScience.pdf). These criteria rank the features according to its contribution to classification performance. The root node is the feature that contributes the most to classification success. In other words, it is the most distinguishing feature. The root node is splitted into the branches according to its categories or values. The root node (internal node) is determined for each branch again.

This process is repeated until a terminal node is reached. As can be understood from here, internal nodes are determined by using the data set which includes the instances providing specified property of its parent node, while root node is determined by using whole data set.

Ensemble Classification Methods: Ensemble classification methods are based on combining of several base classification methods to improve the prediction performance. These methods can be divided into three main categories as bagging, boosting, and stacking (**Figure 2**). General working principle of the ensemble methods can be summarized as follows. In bagging, firstly, N samples, each of with n dimensions are created by using simple random sampling (with replacement) method from original training set (**Figure 2a**). Each sample is trained via a base classifier such as KNN, SVM, Bayes etc. simultaneously. The prediction results are aggregated by using some methods such as weighted average or majority voting. The base classifiers execute independently of each other in bagging. The main idea behind boosting method is to obtain a strong classifier by combining weak classifiers (**Figure 2b**). In this method, a single sample with n dimension is constituted at the beginning of the classification process. The selected base classifier is applied to the sample and misclassified instances are identified. In the next step, a new sample is created by assigning higher weights to misclassified instances. Base classifier is applied to new sample and misclassified instances are determined again. The weights of misclassified instances are increased. This process is repeated until the predetermined number of repetitions or the desired training error is reached. As a result of the process, a high-performance classifier is obtained by combining the weak classifiers. As can be understood, the boosting is a method working sequentially while the bagging is method working parallelly. The bagging and boosting have in common is that they both use the same base classifier during the classification process. The stacking ensemble method (**Figure 1**) directly works on the original training set without creating sub-samples. The training set is learned by using different types of base classifiers and classification results are combined by using a meta-classifier.

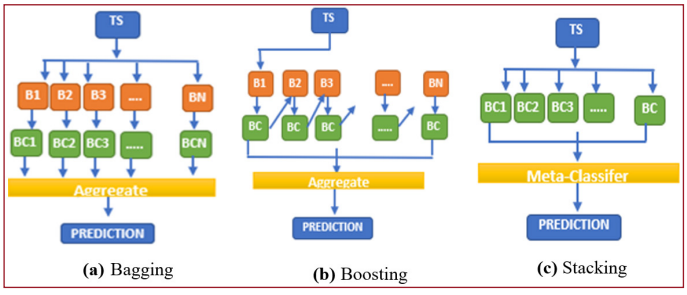

Figure 1. Ensemble Methods

In this study, 7 base classifiers and 23 ensemble classifiers are used. The reason of using numerous classifiers is to identify the predictive model best reflecting the relationship between the hematological and biochemical markers and the bacteremia.

Evaluation Criteria

A confusion matrix is utilized to compare and evaluate the performance of classification methods. The confusion matrix is given as in **Figure 2** for our study.

		Predicted Class	
		Nonbacteremic	Bacteremic
Actual Class	Nonbacteremic	True Negatives (TN)	False Positives (FP)
	Bacteremic	False Negatives (FN)	True Positives (TP)

Figure 2. Confusion Matrix

In **Figure 2**, TN is the number of participants who are classified as non-bacteremic while non-bacteremic in actual (correctly classified), FP is the number of participants who are classified as bacteremic while non-bacteremic in actual (incorrectly classified), FN is the number of participants who are classified as a non-bacteremic while is bacteremic in actual (incorrectly classified) and lastly TP is the number of participants who are classified as a bacteremic while is bacteremic in actual. Some evaluation criteria obtained by using confusion matrix can be given as follows [15]:

$$Accuracy\ (Acc) = \frac{TP + TN}{TN + FP + FN + TP} \quad (1)$$

$$Precision = \frac{TP}{TP + FP} \quad (2)$$

$$Recall = \frac{TP}{TP + FN} \quad (3)$$

$$_{F}-Measure\ (F) = \frac{2 * Precision * Recall}{Precision + recall} \quad (4)$$

$$True\ Positive\ Rate\ (TPR) = \frac{TP}{TP + FN} \quad (5)$$

$$False\ Positive\ Rate\ (FPR) = \frac{FP}{FP + TN} \quad (6)$$

AROC is also used to evaluate the performance of the classification methods. AROC refers to the area under the curve obtained by plotting the TPR against the FPR The closer the ACC, Precision, Recall, F-Measure, AROC, and TPR values of a classification method are to 1, the higher the classification success. It is desirable that the FPR be close to 0. In this study, ACC, F, and AROC performance metrics are used to compare the classification methods used.

Test Set Selection

Classification consists of two main steps as training and testing. In training step, classification model is predicted by utilizing the relationship between independent and dependent (class) variables. Test step includes evaluating the performance of predicted classification model. Data

set firstly should be divided into two distinct subsets as training set and test set to perform these steps. Thus, test set selection is important subject in the classification. Two methods have been widely used as Hold-out and k-fold cross-validation for this objective. In the Hold-out method, training percentage firstly is determined and the instances in the determined percentage of the data set constitute the training set, the remaining part the test set. In the k-fold cross validation method, data set is firstly divided into k subsets. Hold-out method is repeated ask times such that each time a subset is selected as test set and remaining k-1 subset sets as training set. **Figure 3** illustrates k-5-folds cross validation method.

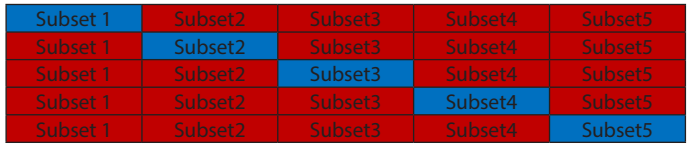

Figure 3. 5-fold cross validation

In **Figure 3**, subsets with blue color indicate the test sets, subsets with red color the training sets. According to **Figure 3**, Subset1 is selected as test set, remaining part (Subset2 + Subset3+ Subset 4+ Subset 5) training in the first execution of the algorithm. In the second execution, Subset 2 is selected as test set, remaining part training (Subset1+ Subset3+ Subset4+ Subset5) set. This procedure is repeated until each subset is the test set once.

Experimental Setup

This section consists of three subsections. First subsection gives the brief information about the statistical properties of the data set. In Subset 2, methods having the highest classification performance based on the cross-validation are determined. Subsect 3 provides the results of feature importance.

RESULTS

Statistical Properties of Data Set

The data set contained a percentage of 2.38% missing values. Missing values were predicted using the KNNImputer method. This study aims to predict the blood culture positivity by using the classification from machine learning algorithms. For this objective, we collected 162 patients' data with diagnosing of acute brucellosis, 54.9% (n=89) of whom are in blood culture negativity group (labelled as 0), 45.1% (n=73) in blood culture positivity group (labelled as 1), 54.9% (n=89) female and 45.1% (n=73) male. The patients in the blood culture negativity group of 41.6% (n=37) were female, 58.4 % (n=52) male, the patients in the blood culture positivity group of 49.3% (n=36) were female, 50.1% (n=37) male. 20 features relating to these participants were studied. The mean± standard deviation of the features is given in **Table 1**.

Table 1. Descriptive Statistics

Features	Overall	0 (n=89)	1 (n=73)	p
Age	39.13±14.76	40.28±15.43	37.72±13.99	0.36
WBC	7067.21±2889.26	7756.22±2756.38	6227.17±2842.24	0.00
HGB	13.06±1.66	13.19±1.57	12.91±1.76	0.28
HCT	38.97±5.10	39.07±5.52	38.85±4.55	0.79
NEUT	4052.30±2451.43	4725.87±2567.68	3231.10±2033.54	0.56
NEUT %	54.11±12.89	58.67±12.15	48.52±11.56	0.00
LYMP	2343.98±913.38	2192.40±801.17	2528.77±1008.96	0.02
LYMP %	34.89±12.06	30.21±10.90	40.59±10.95	0.00
MO %	9.19±2.85	8.91±3.00	9.53±2.64	0.16
EOZ %	1.54±1.61	2.02±1.85	0.94±0.95	0.00
PLT	245.51±81.33	249.06±74.17	241.18±90.05	0.54
CRE	0.78±0.27	0.74±0.15	0.82±0.37	0.16
AST	37.69±44.39	28.20±26.17	49.25±57.64	0.00
ALT	35.93±32.59	27.99±28.11	45.62±35.17	0.00
T. BİL	0.64±0.36	0.59±0.33	0.69±0.40	0.02
D.BİL	0.28±0.16	0.26±0.13	0.31±0.18	0.02
LDH	308.81±192.93	268.92±86.77	357.45±263.93	0.00
FER	306.69±383.61	238.11±269.88	390.30±476.60	0.00
CRP	3.08±3.81	2.57±4.10	3.69±3.35	0.00

*WBC: White blood cell, HGB: Hemoglobin, HCT: Hematocrit, NEUT: Neutrophil, NEUT%: Neutrophil %, LYMP: Lymphocyte, LYMP %: Lymphocyte %, MO %: Monocytes %, EOZ %: Eosinophil %, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, T.BİL: Total bilirubin, D.BİL: Direct bilirubin, LDH: Lactate dehydrogenase, FER: Ferritin, CRP: C-reactive protein

As can be seen in **Table 1**, the mean of WBC, NEUT%, and EOZ% values are significantly higher in the non-bacteremic class. The mean of LYMP, LYMP%, AST, ALT, T.BİL, D.BİL, LDH, FER and CRP are significantly higher than in the bacteremic class. **Figure 4** denotes the box plot of the features for each class.

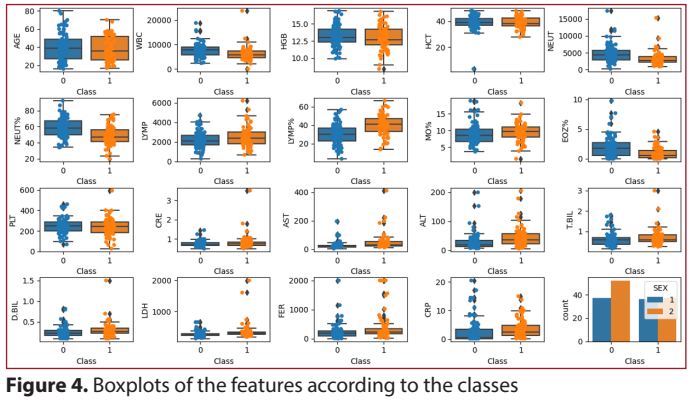

Figure 4. Boxplots of the features according to the classes

Boxplot provides visualization of the distribution of the data. The lines in the middle of the boxes correspond to the median. The start and the finish lines of the boxes represent the first (Q_1) and third (Q_3) quartiles. The difference between two horizontal lines (whiskers) is a measure of heterogeneity in data and is generally calculated as [Q_1-1.5x (Q_3-Q_1) Q_3+1.5x(Q_3-Q_1)]. The instances outside of the horizontal lines represent the outliers. According to this, the medians of Age, WBC, HGB, HCT, NEUT, NEUT%, EOZ%, and PLT are higher in the non-bacteremic class, while the medians of the other features in

the bacteremic class. When the outliers are not considered, the spread of age, WBC, HCT, NEUT, NEUT%, MO%, and EOZ% are higher in the non-bacteremic class, the spread of HGB, LYMP, LYMP%, PLT, CRE, AST, and ALT are higher in the bacteremic class.

Model Development

We utilized the Python environment and Scikit-learn library for executing the classification methods. 30 classifiers, 7 of which are based, 23 of which are ensemble were included in this study. The classification methods, their abbreviations, and forms of usage were given in **Appendix 1**. The cross-validation test set selection method was used, and the number of folds was selected as 15. ACC, F, and AROC were calculated for all folds and classification methods. **Figure 5** shows the box plot of Acc, F, and AROC values obtained from 15 folds.

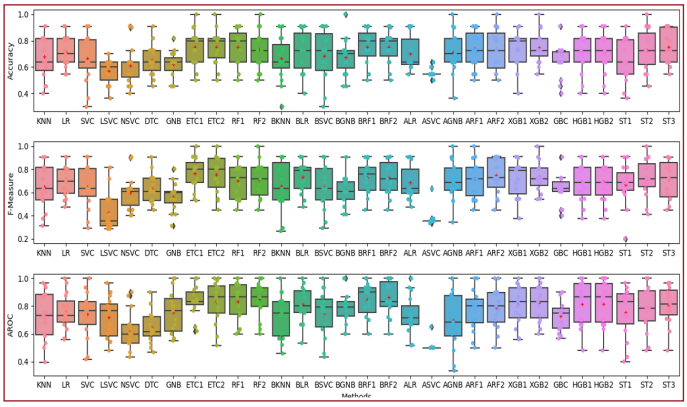

Figure 5. Boxplot of 15- fold cross validation Acc, F and AROC of classification methods

Table 2 gives the arithmetic means and 95% confidence interval of performance metrics for all classification methods, separately.

From **Figure 5** and **Table 2**, the highest Acc values were obtained from ETC1, ETC2, RF1, BRF1, BRF2, XGB2, and ST3, the highest F value from ETC1, and the highest AROC value from BF2. The lowest Acc, F, and AROC values were obtained from the ASCV. From these results, it can be said that ETC1, ETC2, RF1, BRF1, BRF2, XGB2, and ST3 generally provided good classification performance, while ASVC had the worst performance. Acc values ranged between 0.4 and 1, F values between 0.375 and 1, and AROC values between 0.48 and 1 in these methods. However, it is observed that the ETC1 is more successful in classification when evaluating three performance metrics, simultaneously.

3.3 Feature Importance

In this subsection, it was determined which features are the most distinctive in predicting bacteremia in brucellosis. For this objective, the feature importance method was used. This method was executed together with ETC1 which was found as the best method in the classification of bacteremia. All feature scores were normalized into a range of 0-1, with a minimum score of 0 and a maximum score of 1. **Figure 6** gives the bar plots of the feature scores obtained.

Table 2. Mean and confidence interval of the performance metrics.

Methods	Mean [95% Confidence Interval]		
	Acc	F	AROC
KNN	0.68 [0.58 0.77]	0.65 [0.54 0.76]	0.73 [0.63 0.83]
LR	0.72 [0.65 0.78]	0.70 [0.62 0.77]	0.76 [0.69 0.83]
SVC	0.66 [0.56 0.76]	0.65 [0.55 0.76]	0.74 [0.65 0.83]
LSVC	0.57 [0.51 0.63]	0.43 [0.34 0.52]	0.72 [0.64 0.80]
NSVC	0.61 [0.53 0.69]	0.60 [0.51 0.68]	0.63 [0.55 0.70]
DTC	0.65 [0.59 0.72]	0.64 [0.57 0.71]	0.65 [0.58 0.71]
GNB	0.62 [0.56 0.68]	0.56 [0.49 0.63]	0.76 [0.67 0.84]
ETC1	0.75 [0.68 0.83]	0.78 [0.69 0.85]	0.84 [0.78 0.90]
ETC2	0.75 [0.68 0.83]	0.75 [0.66 0.84]	0.83 [0.75 0.92]
RF1	0.75 [0.68 0.83]	0.70 [0.62 0.79]	0.83 [0.75 0.91]
RF2	0.73 [0.65 0.82]	0.71 [0.62 0.80]	0.85 [0.78 0.92]
BKNN	0.66 [0.57 0.76]	0.66 [0.54 0.78]	0.73 [0.65 0.82]
BLR	0.73 [0.64 0.82]	0.73 [0.66 0.81]	0.81 [0.74 0.88]
BSVC	0.68 [0.58 0.80]	0.65 [0.54 0.75]	0.75 [0.66 0.84]
BGNB	0.67 [0.60 0.75]	0.61 [0.54 0.68]	0.79 [0.72 0.85]
BRF1	0.75 [0.68 0.83]	0.73 [0.65 0.81]	0.85 [0.78 0.92]
BRF2	0.75 [0.68 0.82]	0.73 [0.65 0.81]	0.86 [0.79 0.93]
ALR	0.70 [0.63 0.78]	0.69 [0.60 0.77]	0.74 [0. 66 0.81]
ASVC	0.56 [0.54 0.57]	0.37 [0.33 0.41]	0.51 [0.49 0.53]
AGNB	0.71 [0.62 0.80]	0.69 [0.60 0.79]	0.70 [0.58 0.82]
ARF1	0.74 [0.66 0.82]	0.72 [0.63 0.81]	0.77 [0.68 0.85]
ARF2	0.73 [0.65 0.82]	0.75 [0.66 0.84]	0.79 [0.71 0.87]
XGB1	0.73 [0.65 0.82]	0.72 [0.63 0.81]	0.81 [0.73 0.89]
XGB2	0.75 [0.68 0.82]	0.73 [0.66 0.81]	0.82 [0.75 0.89]
GBC	0.64 [0.57 0.71]	0.63 [0.56 0.70]	0.73 [0.67 0.79]
HGB1	0.71 [0.62 0.79]	0.69 [0.60 0.78]	0.82 [0.73 0.91]
HGB2	0.71 [0.62 0.79]	0.69 [0.60 0.78]	0.82 [0.73 0.91]
ST1	0.64 [0.55 0.73]	0.67 [0.57 0.76]	0.75 [0.65 0.85]
ST2	0.73 [0.64 0.82]	0.72 [0.63 0.81]	0.78 [0.68 0.86]
ST3	0.75 [0.68 0.83]	0.71 [0.62 0.81]	0.80 [0.73 0.88]

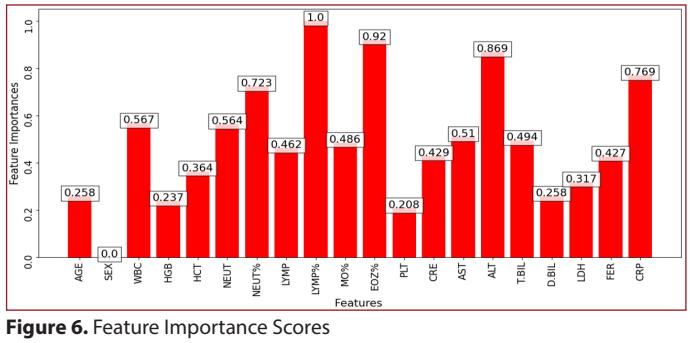

Figure 6. Feature Importance Scores

When examining **Figure 4**, the most distinctive features are NEUT % (0.723), LYMP % (1.000), EOZ% (0.920), ALT (0.869), and CRP (0.769). Besides, the WBC, NEUT, and AST have also moderate importance.

Lastly, in this section, the ETC1 classification method was applied to the data sets including all features and only important features, separately and the confusion matrixes given in **Figure 7**. were obtained.

Appendix1: Classification methods, their abbreviations and form of usage

Classification Methods	Abbreviation	Type	Form of Usage
K-Nearest Neighbor	**Knn**	Base	n_neighbors=10
Logistic Regression	LR	Base	solver='**lbfgs**'
	SVC	Base	decision_function_shape='ovo'
Support Vector Machines	LSVC	Base	LinearSVC()
	NSVC	Base	NuSVC()
Decision Trees	DTC	Base	max_depth=20, random_state=42
Gaussian Naïve **Bayes**	GNB	Base	GaussianNB()
Extra Trees	ETC1	Ensemble	criterion ="**entropy**", max_depth=20, bootstrap=**True**
	ETC2	Ensemble	criterion ="**gini**", max_depth=20, bootstrap=**True**
Random Forest	**Rf1**	Ensemble	criterion='**entropy**', max_depth=20, max_samples=20
	Rf2	Ensemble	criterion='**gini**', max_depth=20, max_samples=20
Bagging	B**Knn**	Ensemble	base_estimator=KNeighborsClassifier(n_neighbors=10), max_samples=0.7,max_features=0.7, n_estimators=20
	BLR	Ensemble	base_estimator=LogisticRegression(solver='**lbfgs**'), max_samples=0.7,max_features=0.7, n_estimators=20
	BSVC	Ensemble	base_estimator=svm.SVC(decision_function_shape='ovo'), max_samples=0.7, max_features = 0.7, n_estimators=20
	BGNB	Ensemble	base_estimator=GaussianNB(), max_samples=0.7,max_features=0.7, n_estimators=50
	B**Rf1**	Ensemble	base_estimator=RandomForestClassifier(criterion='**gini**', max_depth=200, max_samples=50), max_samples=0.7,max_features=0.7, n_estimators=20
	B**Rf2**	Ensemble	base_estimator=RandomForestClassifier(criterion='**entropy**', max_depth=200, max_samples=50), max_samples=0.7,max_features=0.7, n_estimators=20
Adaboost	ALR	Ensemble	base_estimator=LogisticRegression(solver='**lbfgs**'), algorithm="**SAMME**", n_estimators = 100, random_state=**None**
	ASVC	Ensemble	base_estimator=svm.SVC(decision_function_shape='ovo'), algorithm="**SAMME**", n_estimators = 100,random_state=**None**
	AGNB	Ensemble	base_estimator=GaussianNB(), algorithm="**SAMME**", n_estimators = 100,random_state=**None**
	A**Rf1**	Ensemble	base_estimator=RandomForestClassifier(criterion='**gini**', max_depth=50, max_samples=20), algorithm="**SAMME**", n_estimators = 100,random_state=**None**
	A**Rf2**	Ensemble	(base_estimator=RandomForestClassifier(criterion='**entropy**', max_depth=50, max_samples=20),algorithm="**SAMME**", n_estimators = 100,random_state=**None**
XGBoost	XGB1	Ensemble	base_score=0.5,learning_rate=0.2, n_estimators=100, objective='**binary:logistic**', tree_method='**exact**', booster='**gbtree**'
	XGB2	Ensemble	base_score=0.5,learning_rate=0.2, n_estimators=100, objective='**binary:logistic**', tree_method='**exact**',booster='**gblinear**'
Gradient Boosting	GBC	Ensemble	(n_estimators=100, learning_rate=0.2, max_depth=50, random_state=0
Histogram-Based Gradient Boosting	HGB1	Ensemble	loss='**log_loss**'
	HGB2	Ensemble	loss='**binary_crossentropy**'
	ST1	Ensemble	level0.append(('**rf1**', RandomForestClassifier(criterion='**entropy**', max_depth=20, max_samples=20))) level0.append(('**rf2**',RandomForestClassifier(criterion='**gini**', max_depth=20, max_samples=20))) level0.append(('**df1**', DecisionTreeClassifier(max_depth=20, random_state=42))) level1 = ExtraTreesClassifier(criterion ="**gini**", max_depth=20, bootstrap=**True**) s1 = StackingClassifier(estimators=level0, final_estimator=level1, cv=5)
	ST2	Ensemble	level0.append(('**knn**', KNeighborsClassifier(n_neighbors=10))) level0.append(('**cart**', DecisionTreeClassifier(max_depth=20, random_state=42))) level0.append(('**bayes**', GaussianNB())) level1 = RandomForestClassifier(criterion='**gini**', max_depth=100, max_samples=20) s1 = StackingClassifier(estimators=level0, final_estimator=level1, cv=5)
	ST3	Ensemble	level0.append(('**knn**', KNeighborsClassifier(n_neighbors=10))) level0.append(('**cart**', DecisionTreeClassifier(max_depth=20, random_state=42))) level0.append(('**bayes**', GaussianNB())) level1 = RandomForestClassifier(criterion='**gini**', max_depth=100, max_samples=20) s1 = StackingClassifier(estimators=level0, final_estimator=level1, cv=5)

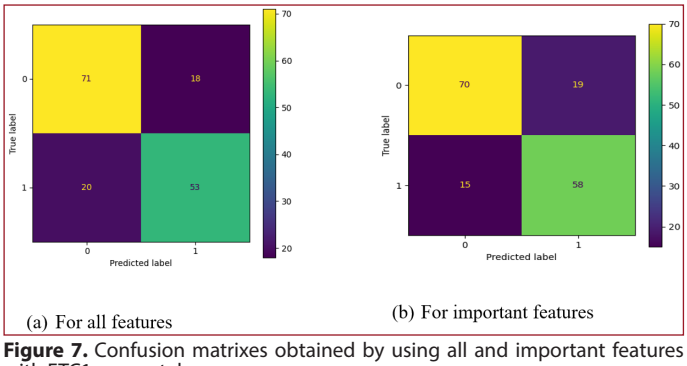

Figure 7. Confusion matrixes obtained by using all and important features with ETC1, separately

As can be seen in **Figure 7**, ETC1 correctly classified 71 of 89 (80%) instances in the non-bacteremic group and 53 of 73 (73%) instances in the bacteremic group when all features were used in the classification. When only important features were considered, the Acc value was found as 0.79. Besides, ETC1 correctly classified 70 of 89 (79%) instances in non-bacteremic and 58 of 73 (79%) instances in bacteremic. As can be understood from this result, the TP rate was increased for the bacteremic group in the second case.

DISCUSSION

Brucellosis is one of the most dangerous zoonotic diseases. It causes significant clinical conditions in humans and leads to a significant loss of productivity in the livestock industry.[16] A definitive diagnosis of brucellosis is the isolation of bacterium from blood, bone marrow or body fluids, and other tissues.[17,18] The presence of bacteremia is important in brucellosis. When serology is negative due to various factors, the diagnosis of brucellosis is supported by a positive culture. In addition, the presence of bacteremia may be important for treatment change in experimental protocols and appears to provide an increased risk for relapse of the disease. The presence of bacteremia is synonymous with the development of secondary seeding and focal complications.[7,19] There may be clinical and laboratory differences in brucellosis patients with and without bacteremia. Kaduna et al.[7] found that AST, ALT elevation, and leukopenia were to be higher in bacteremic patients than in non-bacteremic patients. In the study of Qie et al.[20] thrombocytopenia and CRP elevation were found to be higher in bacteremic patients. In a study conducted on pediatric patients with a diagnosis of brucellosis, high CRP, ALT, and AST levels were found to be important markers for blood culture positivity drawing a conclusion that lower hemoglobin, iron, and vitamin D levels and higher leukocyte, CRP, and ferritin levels were associated with blood culture positivity rate. In these studies, the statistical characteristics of the laboratory findings of the patients were generally emphasized to identify important biomarkers in distinguishing between bacteremic and non-bacteremic patients.[21,22] Recently, classification, which is one of the machine learning methods has been widely exploited to diagnose a disease and to determine important features for diagnosing the disease. The correct and early diagnosis of brucellosis is very crucial. The definitive diagnostic test is the blood culture, but it is time-consuming. Therefore, we aimed to investigate whether some hematological and biochemical parameters are useful in predicting bacteremia with the help of the machine learning method, which is one of the artificial intelligence applications.

Some studies about this subject can be summarized as follows: Chicco and Jurman[23] used the RF classification method to diagnose hepatitis C diseases and to determine the most diagnostic features for hepatitis C. They found that RF provided good performance for diagnosing hepatitis C and AST and ALT levels were diagnostic features. Chicco and Oneto[24] applied nine classification methods to a dataset of electronic health records, consisting of 364 patients and 29 features to predict septic shock. As a result of this study, they observed that the NB classifier had the highest accuracy value, and creatinine, Glasgow coma scale, mean arterial pressure, and initial procalcitonin were the most diagnostic features to predict septic shock.[24] Xiong et al.[25] employed RF, SVM, and LR classification methods to predict the severity of illness of COVID-19 patients at the time of hospital admission and to identify the most important features in distinguishing severe COVID-19 patients. The dataset used in this study consists of 23 features and a total of 287 patients, 36.6% of whom were severe cases and 63.4% of whom were non-severe cases. They concluded that RF yielded the best performance and chest-CT, neutrophil to lymphocyte ratio, lactate dehydrogenase, and D-dimer were important features. Kou et al.[26] proposed a feature representation algorithm to identify the pathogenicity of the influenza B virus. In the study, firstly, 67 RF classifiers were used to determine the informative features. Then, the classification performances of RF, SVM, NB, and KNN were compared based on the optimal features set, and lastly, the RF classifier was selected for pathogenicity identification of IBV according to evaluation criteria. Herein we aimed to predict the classification of bacteremia in patients with acute brucellosis based on some hematological and biochemical markers. Besides, it investigated the most important hematological and biochemical features in predicting bacteremia. The main objective of this study is to decide faster whether the patients are bacteremic or not by identifying the important features indicating the existence of bacteremia. To our best knowledge, this study is the first study conducted for this topic.

To achieve this objective, a dataset consisting of 162 patients with a diagnosis of acute brucellosis, 89 (54.9%) of whom has non-bacteremic, 73 (45.1%) bacteremic, and 20 features including age, sex, and 18 hematological and biochemical markers were collected retrospectively. 30 classification methods, 7 of which were base classifiers, and 23 of which were ensemble classifiers were applied to the collected bacteremia data set. Firstly, statistical

characteristics of the features used were examined according to a class of bacteremia. The mean of WBC, NEUT% and EOZ% values were significantly higher in the non-bacteremic group. The mean of LYMP, LYMP%, AST, ALT, T.BIL, D.BIL, LDH, FER, and CRP levels were significantly higher than in the bacteremic group. In the second step, the classification process had been performed for each method separately and the method providing highest classification performance was determined according to three performance metrics. According to means of the performance metrics, it was decided that ETC1 had the highest classification performance. The means of ACC, F, and AROC values were found as 0.75, 0.78, and 0.84 for ETC1, respectively. To determine the most distinguishing features in the classification of bacteremia, feature importance was used. The normalized feature importance scores were found as 0.723, 1.000, 0.93, 0.869, and 0.769 for NEUT %, LYMP %, EOZ %, ALT, and CRP, respectively. It concluded that the most important feature was the LYMP %. Besides, it was observed that the WBC, NEUT, and AST had also moderate importance. Lastly, ETC1 was applied to the data sets including all features and only important features separately, the results were evaluated by utilizing the confusion matrix. When considering all features simultaneously, ETC1 correctly classified 71 of 89 (80%) instances in the non-bacteremic group and 53 of 73 (73%) instances in the bacteremic group. When the ETC1 was executed by considering only the important features, 70 of 89(79%) instances in the non-bacteremic group and 58 of 73(79%) instances in the bacteremic group were correctly classified. As a result of the study, it was observed that the high levels of LYMP %, ALT, and CRP and low levels of NEUT% and EOZ% can indicate bacteremia in brusellosis.

Limitations

This study is a single center, had limited number of patients and retrospective design.

CONCLUSIONS

The definitive diagnosis of brucellosis is the isolation of Brucella spp. in blood or bone marrow culture. However, despite technological developments, the growth of bacteria in culture and identification after growth is time-consuming. For all that, the levels of some laboratory biomarkers may differ in bacteremic and non-bacteremic patients, and we used the machine learning algotritms to predict bacteremia in brucellosis. Our results showed that the ETC1 classifier can be used as a predictive tool for bacteremia in brucellosis patients based on hematological and biochemical parameters. The feature importance method was used for determining the most distinguishing features of bacteremia. It is concluded that the most important feature was the LYMP% and that the WBC, NEUT, and AST have also moderate importance, and that high levels of LYMP %, ALT and CRP, and low levels of NEUT %, and EOZ % are parameters that can predict bacteremia.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was supported by the Clinical Research Ethics Committee of Harran University with the number 22.10.21 on May 23, 2021.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Evaluation of the Relationship between Favipiravir Use Status and Telogen Effluvium in Patients Diagnosed with COVID-19

COVID-19 Tanısı Alan Hastalarda Favipiravir Kullanım Durumu ile Telogen Effluvium Arasındaki İlişkinin Değerlendirilmesi

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Abstract

Aim: Favipiravir (FVP) is a competitive inhibitor of viral RNA-dependent RNA polymerase and is also a purine nucleoside analogue. It produces antiviral activity against the SARS-CoV-2 virus and has been used to treat COVID-19. Telogen effluvium (TE) is a widespread, non-scarring shedding due to the early entry of hair during the telogen phase. The most prevalent causes are drugs, physiological and emotional stress, surgery, high fever, chronic infections, diet, iron deficiency, and smoking. In this study, we investigated whether there was a significant difference in terms of TE by questioning the patients who had coronavirus in the last 1 year, and who received and did not receive FVP treatment.

Material and Method: Patients between the ages of 18 and 65, who applied to the Dermatology and Venereal Diseases Outpatient Clinic of Karaman Training and Research Hospital with a complaint of hair loss and who were diagnosed with COVID-19 over the past year, were included in this study. We confirmed the diagnosis of TE by using trichoscopy on patients with a positive pull test. We investigated whether there was a difference in terms of TE and other types of hair loss between patients who received FVP treatment and those who did not. For the study Karamanoglu Mehmet Bey University ethics committee approval was obtained (June 29, 2022).

Results: As a result of comparing the patients' gender, comorbidity, pull test, and trichoscopic findings according to the use of FVP, it was clear that most of the FVP users were women (p=0.027). Among those who did not use FVP, positive pull test scores were significantly higher (p=0.026). The fact that the pull test was significantly lower in patients in our study using FVP may suggest that FVP has no effect on TE's development.

Conclusion: We found no studies on the effect of FVP on alopecia and TE. We believe that the use of FVP reduces the positivity of the pull test, therefore, its effect on hair loss may be related to non-TE alopecia. We believe that our study is also important in this regard.

Keywords: Favipiravir, Telogen effluvium, COVID-19

Öz

Amaç: Favipiravir (FVP), viral RNA'ya bağımlı RNA polimerazın yarışmalı bir inhibitörüdür ve aynı zamanda bir pürin nükleozid analoğudur. SARS-CoV-2 virüsüne karşı antiviral aktivite üretir ve COVID-19'u tedavi etmek için kullanılmıştır. Telogen effluvium (TE), telogen faz sırasında saçın erken gelişimine bağlı olarak yaygın bir dökülmedir. En yaygın nedenler; ilaçlar, fizyolojik ve duygusal stres, ameliyat, yüksek ateş, kronik enfeksiyonlar, diyet, demir eksikliği ve sigaradır. Bu çalışmada son 1 yıl içinde COVID-19 tanısı almış olup, FVP tedavisi alan ve almayan hastaları sorgulayarak TE açısından anlamlı bir fark olup olmadığını araştırdık.

Gereç ve Yöntem: Bu çalışmaya Karaman Eğitim ve Araştırma Hastanesi Deri ve Zührevi Hastalıklar polikliniğine saç dökülmesi şikayeti ile başvuran ve son bir yıl içinde COVID-19 tanısı konan 18-65 yaş arası hastalar dahil edildi. Pull testi pozitif olan hastalarda trikoskopi kullanarak TE tanısını doğruladık. FVP tedavisi alan ve almayan hastalar arasında TE ve diğer saç dökülme tipleri açısından fark olup olmadığını araştırdık. Çalışma için Karamanoğlu Mehmet Bey Üniversitesi etik kurul onayı alındı (29 Haziran 2022).

Bulgular: Hastaların cinsiyet, komorbidite, pull testi ve trikoskopik bulgularının FVP kullanımına göre karşılaştırılması sonucunda FVP kullananların çoğunun kadın olduğu görüldü (p=0.027). FVP kullanmayanlar arasında pozitif pull testi oranı anlamlı olarak daha yüksekti (p=0.026). Çalışmamızda FVP kullanan hastalarda pull testinin anlamlı olarak daha düşük olması, FVP'nin TE gelişimi üzerinde etkisinin olmadığını düşündürebilir.

Sonuç: FVP'nin alopesi ve TE üzerine etkisi ile ilgili herhangi bir çalışmaya rastlamadık.FVP kullanımının pull testi pozitifliğini azalttığını bu nedenle saç dökülmesi üzerine etkisinin TE dışı alopesilerle ilişki olabileceğini düşünüyoruz. Çalışmamızın bu açıdan da önemli olduğunu düşünüyoruz.

Anahtar Kelimeler: Favipiravir, Telogen effluvium, COVID-19

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INTRODUCTION

The causative pathogen of COVID-19, which has resulted in the current worldwide pandemic beginning in December 2019, is SARS-CoV-2.[1] Favipiravir (FVP) is a competitive inhibitor of viral RNA-dependent RNA polymerase and is also a purine nucleoside analogue. It produces antiviral activity against the SARS-CoV-2 virus and has been used to treat COVID-19.[2] Cutaneous side effects associated with FVP are rare and include pruritus, rash, and eczema in <0.5% of patients.[3] Telogen effluvium (TE) is a widespread, non-scarring shedding due to the early entry of hair during the telogen phase. Kligman first described it in 1961.[4] The most prevalent causes are drugs, physiological and emotional stress, surgery, high fever, chronic infections, diet, iron deficiency, and smoking. Classic TE, which develops approximately 3-4 months after a triggering condition and is self-limiting, lasts less than 6 months. Forms exceeding 6 months have been reported as chronic TE.[4] In this study, we investigated whether there was a significant difference in terms of TE by questioning the patients who had coronavirus in the last 1 year, and who received and did not receive FVP treatment.

MATERIAL AND METHOD

18-65 years old patients are included in this study who applied to the Karaman Training and Research Hospital, Dermatology, and Venereal Diseases outpatient clinic complaining of hair loss and having had COVID-19 in the last year. Those who received and did not receive FVP treatment were determined and recorded. The patients involved in the study provided informed consent, and the pull test was performed from the places where hair loss was most active. In the pull test, about 50 strands of hair were pulled lightly without hurting and the presence of five (10%) or more hairs on the hand showed that telogen was active.[5-7] Trichoscopy is a noninvasive method in which the scalp is examined with a dermatoscope. Although it is recommended to use a video dermatoscope in trichoscopic examinations because of the high resolution—magnifying the image 20-1000 times—it is not always possible and practical to use the video dermatoscope because it is not portable. The hand dermatoscope, which provides ten times magnification, can magnify 30 times with the help of a digital camera. This pocketable device is much cheaper than a video dermatoscope and has proven to be as successful in diagnosing alopecia.[8-11] We also confirmed the diagnosis of TE by using trichoscopy on patients with a positive pull test. Routine laboratory tests, such as complete blood count, thyroid function tests, vitamin D levels, ferritin, B12, and folic acid were requested from patients with a confirmed diagnosis of hair loss, and the underlying secondary causes were recorded.[12,13] We investigated whether there was a difference in terms of TE and other types of hair loss between patients who received FVP treatment and those who did not. For the study Karamanoglu Mehmet Bey University ethics committee approval was obtained.

Statistical Analysis

The data were analyzed using the SPSS 25.0 package program. Continuous variables were given as mean±standard deviation, and categorical variables were given as numbers and percentages. Significance test of the difference between two means in comparison of independent group differences when parametric test assumptions are met; when parametric test assumptions were not met, the Mann-Whitney U test was used to compare the independent group differences. In dependent group comparisons, when the parametric test assumptions were met, a significance test was conducted of the difference between the two spouses. The Wilcoxon paired-sample test was used when parametric test assumptions were not met. In addition, the relationships between continuous variables were analyzed using Spearman or Pearson correlation analyses and the differences between categorical variables were analyzed using the Chi-square analysis.

RESULTS

The mean age of 100 patients was 32±10 years, and 62% were female. Nineteen percent of the participants had an additional chronic disease (six people with diabetes mellitus, three with hypertension, two with asthma, four with thyroid disease, one with a psychiatric disease, one with seborrheic dermatitis, one with ankylosing spondylitis, and one with PCOS). Fourteen percent regularly used medication. Ten percent had an additional dermatological disease (five with androgenic alopecia, two with maculopapular eruptions, one with herpes labialis, one with psoriasis, and one with urticaria). Forty-nine percent of the patients used FVP. As a result of comparing the patients' gender, comorbidity, pull test, and thyroscopic findings according to the use of FVP, it was clear that most of the FVP users were women (p=0.027). Among those who did not use FVP, positive pull test scores were significantly higher (p=0.026) (**Table 1**).

Table 1. Comparison of patients' gender, comorbidity, PULL test and trichoscopy findings according to FVP use

	FVP						p
	Not used		Used		Total		
	N	%	N	%	N	%	
Gender							0.027
Female	25	51.0	37	72.5	62	62	
Male	24	49.0	14	27.5	38	38	
Additional diagnosis							0.374
No	45	91.8	44	86.3	89	89	
Yes	4	8.2	7	13.7	11	11	
PULL							0.026
Negative	10	20.4	22	43.1	32	32	
Positive	39	79.6	29	56.9	68	68	
Trichoscopy							0.051
No finding	17	35.4	19	37.3	36	36	
Yellow dots	16	33.3	17	33.3	33	33	
Empty follicles.	15	31.3	15	29.4	30	30	

*Mann-Whitney U test FVP: Favipiravir

As a result of the comparison of the age and laboratory values of the patients according to the use of FVP, we did not find any difference in age and laboratory values between those who used and did not use FVP (**Table 2**).

Table 2. Comparison of the age and laboratory values of the cases according to the use of FVP

	FVP				Total		p*
	Not used		Used				
	Mean	SD	Mean	SD	Mean	SD	
Age	32	10	34	11	33	11	0.790
Hb	14	2	13	2	14	2	0.156
B12	422	138	433	166	427	152	0.761
Folic acid	14.2	8.5	17.9	29.5	16.1	22.0	0.955
Iron	67	33	75	38	71	36	0.240
TSH	2	1	2	1	2	1	0.750
Ferritin	34	36	27	27	31	32	0.213
D vit	25	19	22	9	24	15	0.702

SD:Standart Deviation * Mann-Whitney U test Hb:Hemoglobin TSH: Thyroid stimulating hormone FVP: Favipiravir

In addition, comparing laboratory values within normal limits and outside of normal limits according to FVP use showed no significant difference (**Table 3**).

Table 3. Comparison of the laboratory parameters of the cases according to the use of FVP

		FVP				P**
		Not Used		Used		
		N	%	N	%	
Hb	Normal	32	65.3	39	76.5	0.313
	Not Normal	17	34.7	12	23.5	
B12	Normal	47	95.9	51	100.0	0.238
	Not Normal	2	4.1	0	0.0	
Ferritin	Normal	46	93.9	45	88.2	0.264
	Not Normal	3	6.1	6	11.8	
TSH	Normal	49	100.0	51	100.0	NA*
	Not Normal	0	0.0	0	0.0	
Folik asit	Normal	38	77.6	44	86.3	0.191
	Not Normal	11	22.4	7	13.7	
D vit	Normal	26	53.1	33	64.7	0.327
	Not Normal	23	46.9	18	35.3	
Iron	Normal	25	51.0	28	54.9	0.851
	Not Normal	24	49.0	23	45.1	

* no appreciable ** Wilcoxon paired-sample test, Hb: Hemoglobin TSH: Thyroid stimulating hormone FVP: Favipiravir

DISCUSSION

This study investigated whether there was a significant difference in terms of TE by questioning the patients who had COVID-19 in the last year and who had received or not received FVP treatment. In addition, patients were also asked about their diagnosis of chronic dermatological diseases, and it was determined whether there was exacerbation or remission of the lesions after using FVP. Dominguez-Santás et al.[14] has been the first to report the development of acute TE after COVID-19. They described a case of TE occurring 3 months after contracting SARS-CoV-2. Other studies supporting these findings have since been conducted.[15,16] The effects that COVID-19 and FVP—which was widely used in treating COVID-19 had on various dermatological diagnoses, especially TE, were examined. There were significantly more women included in this study than men. This may be related to the fact that TE, which is the most common cause of diffuse hair loss, is more common in women.[17] Iron is an important cofactor in cell DNA, and its deficiency facilitates the development of TE by reducing the proliferation capacity in the hair matrix.[18] Çadırcı et al.[19] reported that 54% of the TE patients in their study had ferritin deficiency, 42% had iron deficiency, and 1% had B12 deficiency. In our study, iron deficiency was detected in 45% of patients using FVP and 49% of patients not using FVP. Hypothyroidism delays the onset of a new anagen phase by inducing the catagen phase. In this way, TE can develop. The mechanism of hair loss in hyperthyroidism is not clear.[20] In our study, these values were similar between patients who used FVP and those who did not. There is no clear consensus on the role of vitamin D in TE. Rasheed et al.[21] reported that serum 25 hydroxyvitamin D levels were significantly lower in female patients with a diagnosis of chronic TE when compared to healthy controls. On the other hand, there are also studies stating that the development of TE and vitamin D levels are unrelated.[22] In this study, vitamin D levels were similar between patients who used FVP and those who did not. The results suggest that more studies are needed in order to examine the role of vitamin D levels in both acute and chronic TE. A study conducted in Thailand reported that cutaneous side effects developed in five patients who had COVID-19 and received FVP treatment, two of which were diagnosed with maculopapular eruption, two with urticaria, and one with Stevens-Johnson syndrome. They stated that the time between FVP treatment and the onset of rash was 7 days. The mean duration of the rash was 5 days.[23] In another study, acute generalized exanthematous pustulosis was reported in a patient treated with FVP.[24] Çeviker et al.[25] reported that urticaria and angioedema developed on the 3rd day of FVP treatment in a 55-year-old female patient who was followed-up with for COVID-19 pneumonia. Maculopapular eruption developed after FVP use in three patients included in our study, and a 61-year-old male patient developed an urticaria attack that developed on the 4th day of FVP use and required a change in treatment. This may be a rare side effect of FVP or a cutaneous marker of COVID-19, and this distinction is not clear.Although TE is not a specific trichoscopic finding, decrease in hair density, empty follicles, and yellow spots are visible drums. There is an increase in the number of follicular units containing a single hair. Newly growing hair has a pointed, hard, and pigmented body.[8,10,11] In our patients, yellow spots and empty follicles were found among trichoscopic findings. Trichoscopic findings did not differ significantly between patients using and not using FVP. It is important to remember that androgenic alopecia and TE may coexist in many female patients. In our study, androgenic

alopecia was present in four female patients. Rossi et al.[26] examined TE cases that developed after the patient had COVID-19. This study emphasized that treatments for COVID-19 and stress are not important triggers in developing acute TE, and the most important factor in its development is the SARS-CoV-2 infection itself. The fact that the pull test was significantly lower in patients in our study using FVP may suggest that FVP has no effect on TE's development. Studies on the cutaneous side effects of the drug were examined, and we did not find any study on its effect on alopecia and TE. We think that our study is also important in this respect.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for this study, dated 29.06.2022 and numbered 06-2022/09, was obtained from the clinical research ethics committee of Karamanoğlu Mehmet Bey University, Faculty of Medicine.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Diagnostic Value of Target Sign and Apparent Diffusion Coefficient Measurements in the Differentiation between Hepatocelular Carcinoma and Liver Metastasis on Diffusion Weighted Magnetic Resonance Imaging

Difüzyon Ağırlıklı Manyetik Rezonans Görüntülemede Hepatoselüler Karsinom ve Karaciğer Metastazı Ayırımında Hedef İşaretinin ve Görünür Difüzyon Katsayısı Ölçümlerinin Tanısal Değeri

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Abstract

Aim: The aim of our study is to investigate probable differences between the incidence of target sign detected by diffusion-weighted magnetic resonance imaging (DWI) and apparent diffusion coefficient (ADC) values between liver metastases and hepatocellular carcinomas (HCC).

Material and Method: A total of 155 lesions obtained from 57 (female/male: 18/39) patients were included in the study. Dimensions of lesions, the appearance of lesions detected by DWI, minimum ADC (ADCmin) values, and average ADC (ADCav) values were evaluated with 1.5 Tesla MRI using b= 0 and b=1000 s/mm² values. Differences between metastases and HCC were investigated in terms of defined parameters. Also, ROC (receiver operating curve) analysis was used to evaluate the performance of ADCmin and ADCav parameters in distinguishing metastases from HCC.

Results: Of the lesions, 131 were metastases, while 24 were HCC. The image showing centrally hypointense, periphery hyperintense signal in DWI defined as target sign. Target sign detected in 72 metastatic lesions (55%) and 6 HCC lesions (25%) with DWI, and the rate of target sign detection was higher in the metastatic group compared with HCC ($p<0.007$). Also, ADCmin and ADCav values were found to be higher in the HCC group compared with the metastatic group ($p<0.001$). Based on ROC analysis optimal ADCmin and ADCav values were $<758\times10^{-6}$ and $<817\times10^{-6}$ mm²/s, respectively, in distinguishing metastasis from HCC (Sensitivity: 0.412, 0.412; Specificity: 0.875, 0.917 respectively).

Conclusion: Target sign detected by DWI and ADC values can be used as MRI markers that enhance diagnostic accuracy in distinguishing between liver metastases and HCC.

Keywords: Target sign, diffusion-weighted magnetic resonance imaging, metastasis, hepatocellular carcinoma

Öz

Amaç: Çalışmamızın amacı, karaciğer metastazları ve hepatoselüler karsinom (HCC)'da difüzyon ağırlıklı manyetik rezonans görüntüleme (DWI) ile tespit edilen hedef işaret insidansı ve görünür difüzyon katsayısı (ADC) değerleri arasındaki olası farklılıkları araştırmaktır.

Gereç ve Yöntem: 57 (kadın/erkek: 18/39) hastadan elde edilen toplam 155 lezyon çalışmaya dahil edildi. Lezyonların boyutları, DWI ile tespit edilen lezyonların görünümü, minimum ADC (ADCmin) değerleri ve ortalama ADC (ADCav) değerleri, b= 0 ve b=1000 s/mm² değerleri kullanılarak 1,5 Tesla MRG ile değerlendirildi. Tanımlanan parametreler açısından metastazlar ve HCC arasındaki farklar araştırıldı. Ayrıca metastazları HCC'den ayırmada ADCmin ve ADCav parametrelerinin performansını değerlendirmek için ROC analizi kullanıldı.

Bulgular: Lezyonların 131'i metastaz, 24'ü HCC idi. Hedef işareti olarak tanımlanan, DWI'da merkezi hipointens, periferik hiperintens izlenen imaj DWI ile 72 metastatik lezyonda (%55) ve 6 HCC lezyonunda (%25) saptandı ve metastatik grupta hedef işareti saptanma oranı HCC'ye göre daha yüksekti ($p<0,007$). Ayrıca HCC grubunda, ADCmin ve ADCav değerleri metastatik gruba göre daha yüksek bulundu ($p<0.001$). ROC analizine dayalı olarak, metastazı HCC'den ayırmada optimal ADCmin ve ADCav değerleri sırasıyla $<758\times10^{-6}$ ve $<817\times10^{-6}$ mm²/s idi (Duyarlılık: 0.412, 0.412; Özgüllük: sırasıyla 0.875, 0.917).

Sonuç: DWI ile saptanan hedef işareti ve ADC değerleri, karaciğer metastazı ve HCC ayrımında tanısal doğruluğu artıran MRI belirteçleri olarak kullanılabilir.

Anahtar Kelimeler: Hedef İşareti, difüzyon ağırlıklı manyetik rezonans görüntüleme, metastaz, hepatosellüler karsinom

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INTRODUCTION

Metastases are the most frequent liver masses, and dynamic contrast-enhanced magnetic resonance imaging (MRI) has an important role in the diagnosis of liver metastases.[1] However, conditions in which contrast agents are contraindicated and probable side effects caused by contrast agents limit the use of contrast-enhanced imaging methods.[2-5] In studies in recent years, it has been stated that addition of diffusion-weighted MRI (DWI) to the MRI protocol enhances the rate of diagnostic accuracy, and DWI can be used as an assisting imaging method.[5,6]

DWI is an effective and practical MRI technique that is based on the free motion of water molecules. It does not require contrast agent use, and it is quickly completed. As is well known, metastatic masses exhibit diffusion limitations in DWI because of their high cellular content. The degree of diffusion restriction can be quantitatively expressed using apparent diffusion coefficient (ADC) measurements.[5-8] General condition failures and contraindications of contrast agent use are more frequently observed in metastatic patients. Thus, the use of DWI, which does not require a contrast agent, becomes crucial in this patient group.[4] In the literature, there are various studies on the evaluation of metastases using DWI. However, in most of these studies, metastases were evaluated together with other lesions under the title of focal liver masses, and ADC measurements were taken into account in the evaluations.[9-19] In recent years, target sign appearance, which is formed based on signal properties of liver masses in DWI sequences, was defined in several studies.[20-22] In these studies, it was stated that target sign on DWI was observed more frequently in intrahepatic cholangiocellular carcinoma (ICC) compared with hepatocellular carcinoma (HCC) and hypovascular solitary metastases. In our opinion, there is not a study in the literature that investigates differences in the incidence of target sign detected by DWI between metastatic liver lesions and hepatocellular carcinoma (HCC), which is the most frequent primary liver mass.[23] Therefore, our aim is to investigate probable differences in target sign on DWI and ADC values between metastases and HCC.

MATERIAL AND METHOD

Study Population

The study started after obtaining ethics committee approval from Clinical Investigations Ethics Committee of Tokat Gaziosmanpaşa University Medical Faculty (21.12.2020 /16-KAEK-057). The study was financially supported by the Scientific Research Projects Unit of Tokat Gaziosmanpaşa University Medical Faculty. Patients with a liver mass and with a diagnosis of metastasis or HCC were included in the study, and these patients were imaged using upper abdominal diffusion MRI. The diagnoses was determined using histopathological sections obtained from liver lesions. All patients gave informed written consent. Age and gender data and histopathological evaluation reports of patients were collected from the hospital database.

MRI Technique

Patients were imaged with a 1.5 Tesla (T) MRI instrument (Signa Explorer 25.0, General Electric Medical System Waukesha, WI) using 16 channels phased-array body coil. DWI sections were obtained by echo planar diffusion weighted sequences in the axial plan using b= 0 and b=1000 s/mm². DWI parameters were as follows: TR:~ 9000 ms; TE: 91.1 ms; field-of-view (FOV): 410×410 mm; matrix size: 80×128; slice thickness: 7 mm; inter-slice gap: 1.5 mm.

Image Analysis

Analysis of the images was carried out using a workstation (Advantage Workstation Volume Share.7, General Electric Medical Systems, Milwaukee, WI, USA), by two radiologists independent of each other with eight to nine years' experience. Radiologists were blinded to diagnosis of patients and to each other's measurements.

Lesion dimensions were obtained by measuring the largest diameter in the DWI sections. Some lesions were visualized as having a hypointense center and a circular hyperintense periphery in DWI sections and were visualized as having a hyperintense center and a circular hypointense periphery in ADC maps. This sign was defined as target sign both in DWI sections and in ADC map (**Figure 1**). Lesions other than target sign were visualized as diffuse hyperintense in DWI and diffuse hypointense in ADC maps (**Figure 2**) or were visualized with a heterogeneic signal intensity containing hypo- and hyperintense areas (**Figure 3**). Lesions were divided into two groups, those with target sign and others based on DWI signal intensity. Then, ADC measurements were performed by placing a circular region of interest (ROI) in lesions. Measurements were performed in the peripheral hypointense part of the lesion in patients with the target sign, in the hypointense part of the lesion in lesions with heterogeneic signal intensity, and around the periphery of the lesion in completely hypointense lesions. The instrument automatically calculated average (ADCav) and minimum (ADCmin) values as mm²/s after ROIs were placed. Totally 3 measurements were performed on each lesion. The average of these 3 values was accepted as the mean ADCav and ADCmin value. ROI dimensions and obtained ADC values were recorded.

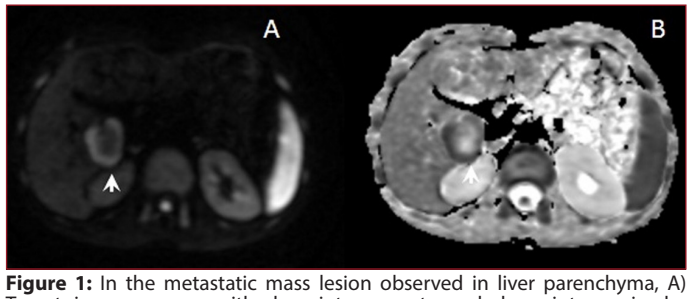

Figure 1: In the metastatic mass lesion observed in liver parenchyma, A) Target sign appearance with a hypointense center and a hyperintense circular periphery in DWI; B) In contrast to DWI, target sign appearance with a circular hypointense periphery and a hyperintense center in an ADC map passing through the same section

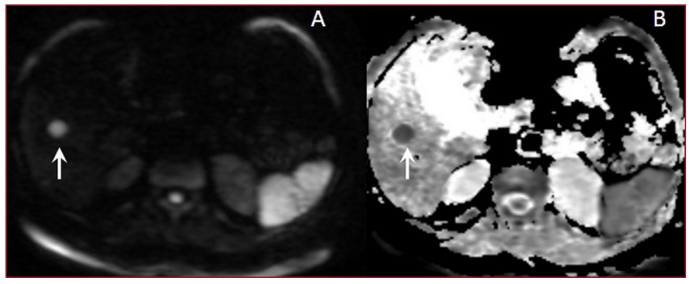

Figure 2: The metastatic mass lesion observed in liver parenchyma A) Diffuse hyperintense appearance in DWI; B) Diffuse hypointense appearance in ADC map passing through the same section

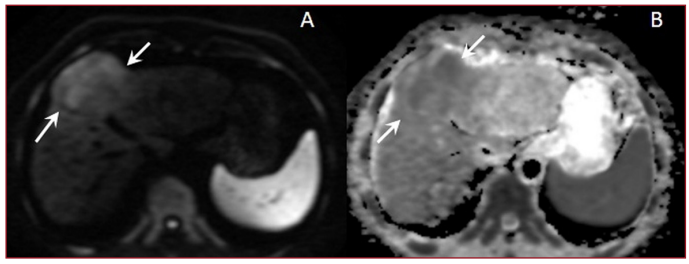

Figure 3: HCC case observed to have hypo-, hyper-, and isointense areas with heterogeneous intensity in both A) DWI; B) ADC map

Statistical Analysis

Complementary analyses were performed in order to give information about general properties of the variables. Continuous variables are given as average±standard deviation; data for categorical variables are given as n (%). Independent sample t test was used to compare the continuous normal data between groups. Cross tabs and chi-square tests were used to compare the categorical data among groups. Receiver operating curve (ROC) analysis was used to evaluate performances of ADCmin and ADCav variables in distinguishing metastases from HCC. Cohen's kappa coefficient was used for interobserver agreement. P-values calculated to be smaller than 0.05 were considered statistically significant. Statistics software was used in calculations (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY).

RESULTS

Fifty-seven patients (female/male: 18/39) were included in the study. The average age was 63.93±10.85 years. Of the 57 patients, 39 had metastatic liver masses, while 18 had HCC. There was not a statistically significant difference in terms of age or gender between the groups (p>0.05). The primary cancers of metastatic patients were as follows in order of frequency: 11 colon (28.2%), 8 lung (20.5%), 6 rectal (15.3%), 6 stomach (15.3%), 3 breast (7.7%), 2 prostate (5.1%), 1 pancreas (2.6%), 1 ovarian (2.6%), and 1 esophagus (2.6%). A total of 155 lesions obtained from 57 patients were evaluated. Of these lesions, 131 were metastases and 24 were HCC. Distribution of quantitative variables based on lesions by groups is given in **Table 1**.

Table 1. Distribution of quantitative variables by group

Variables	Group		p
	Metastasis (n=131)	HCC (n=24)	
Lesion size	29.37±18.59	35.79±25.44	0.248
ROI size (mm)	8.30±1.16	8.28±0.36	0.940
ADCmin ($\times10^{-6}$ mm² /s)	807.83±255.6	1020.42±318.12	<0.001
ADCav ($\times10^{-6}$ mm² /s)	909.03±243.63	1109.98±304.81	<0.001

ROI: region of interest, ADC: apparent diffusion coefficient, Data are given as average±SD, HCC: Hepatocelular carcinoma

With respect to this, ADCmin and ADCav values were significantly lower in the metastasis group compared with the HCC group.

When 155 lesions were evaluated for target sign, target sign was found in 55% of metastases, while this rate was 25% in the HCC group. The difference of the incidence of target sign detection between the two groups was statistically significant (p=0.007) and this ratio was higher in metastases. The distribution of target sign in groups is given in **Table 2**.

Table 2. The distribution of target signs in groups

		Total	Nature of lesion		p
			Target Sign	Others	
	Metastasis	131(84.5)	72(55.0)	59(45.0)	0.007
	HCC	24(15.5)	6(25.0)	18(75.0)	
Primary lesion	Lung	18(11.6)	3(16.7)	15(83.3)	-
	Colon	40(25.8)	20(50)	20(50)	
	Breast	12(7.7)	3(25)	9(75)	
	Stomach	30(19.4)	20(66.7)	10(33.3)	
	Over	2(1.3)	0(0)	2(100)	
	Esophagus	3(1.9)	3(100)	0(0)	
	Pancreas	1(0.6)	0(0)	1(100)	
	Prostate	5(3.2)	5(100)	0(0)	
	Rectal	20(12.9)	18(90)	2(10)	
	HCC	24(15.5)	6(25.0)	18(75.0)	

Data are expressed as frequency or percentage. HCC: Hepatocellular carcinoma

When an evaluation was performed based on the number of patients, the presence of target sign was again significantly higher in the metastasis group (p=0.039) (**Table 3**).

Table 3. The evaluation of the presence of target sign based on the number of patients

		Total	Nature of lesion		p
			Target Sign	Others	
	Metastasis	39(68.4)	20(51.3)	19(48.7)	0.039
	HCC	18(31.6)	4(22.2)	14(77.8)	
Primary lesion	Lung	8(14)	3(37.5)	5(62.5)	-
	Colon	11(19.3)	5(45.5)	6(54.5)	
	Breast	3(5.2)	1(33.3)	2(66.7)	
	Stomach	6(10.5)	4(66.7)	2(33.3)	
	Over	1(1.8)	0(0)	1(100)	
	Esophagus	1(1.8)	1(100)	0(0)	
	Pancreas	1(1.8)	0(0)	1(100)	
	Prostate	2(3.5)	2(100)	0(0)	
	Rectal	6(10.5)	4(66.7)	2(33.3)	
	HCC	18(31.6)	4(22.2)	14(77.8)	

Data are expressed as frequency or percentage. HCC: Hepatocellular carcinoma

ADCmin and ADCav values for distinguishing metastasis from HCC were <758 ×10^{-6} and <817×10^{-6} mm²/s, respectively, with respect to ROC analysis (**Table 4**). Cohen's kappa coefficient (***κ***) is 0.893 (p<0.001) for which measures inter-rater agreement for target sign detection. Correlation coefficients (r) are 0.969 (p<0.001) and 0.934 (p<0.001) for ADCmin and ADCav respectively.

Table 4. ROC analysis results in regard to distinguishing metastasis from HCC

	Cutoff	AUC	Se	Sp	PPV	NPV	p
ADCmin (×10^{-6} mm² /s)	<758	0.680	0.412	0.875	0.947	0.214	0.005
ADCav (×10^{-6} mm² /s)	<817	0.682	0.412	0.917	0.964	0.222	0.005

AUC, area under curve; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value, HCC: Hepatocelular carcinoma

DISCUSSION

This study demonstrates that target sign is observed more frequently in metastasis compared with HCC. Also, ADC values were found to be lower in the metastasis group compared with HCC. These results indicate that target sign detected by DWI and ADC values can be used as MRI markers contributing to differential diagnosis in distinguishing metastasis and HCC.

Target sign detected by DWI was investigated in the evaluation of liver masses in a few studies.[20-22,24] Min et al. found the detection rate of target sign to be higher in ICCcompared with HCC both in hepatobiliary phase-contrast sequences obtained using the liver-specific contrast agent gadoxetic acid and in DWI in their studies.[21] In target sign detected by DWI, the central part was observed to be hypointense and the peripheral part to be hyperintense, as in our study. They stated that central hypointensity detected in DWI might be related to dense collagen, loose fibrotic tissue, or necrosis.[21] Kovač et al. compared hypovascular metastases and ICC in terms of target sign detected in DWI and found that detection rates of target sign were higher in ICC compared with hypovascular metastases. Target sign was also found in a similar appearance, and it was suggested that central hypointensity was the result of fibrous tissue.[20] For the first time in the literature, our study compares metastases and HCC in terms of DWI target sign, and target sign was detected at higher rates in metastases. In our study, metastases were not grouped based on vascularization properties; they were studied as a single group, in contrast to the study by Kovač et al.

Gourtsoyianni et al. noticed a ring-like pattern with a hyperintense central part and a hypointense periphery in ADC maps in colorectal, breast, and lung metastases in their study, in which they compared DWI images and ADC values of benign and malignant focal liver lesions. They indicated that they did not observe such a pattern in pancreatic and intestinal cancer metastases or metastases with an unknown primary tumor and other liver masses. They confirmed that central hyperintensity was related to necrosis using T2 weighted and contrasted T1 weighted sequences.[19] The ring-like appearance described in that study had similar properties with the target appearance. ADC measurements were also performed in the peripheral hypointense part, which was thought to have a cellular content, in lesions with the ring sign, as was done in our study.[19] Gourtsoyianni et al. detected a diffuse hypointense appearance as a second pattern apart from the ring-like pattern in ADC maps. In our study, we detected three different patterns, target sign, diffuse hypointensity, and heterogeneic appearance, in which hypo- and hyperintense regions were found together heterogeneously in ADC maps in metastases and HCC.

Granata et al. evaluated colorectal metastases using gadoxetic acid-MRI sections and detected a target appearance that had a lower degree of hypointensity in the center in 46.7% of lesions. They claimed that the different degree of gadoxetic acid uptake detected in the center of the lesion resulted from interstitial diffusion of the contrast agent in the central necrosis area. They suggested that a comparative evaluation with DWI should be performed to support this hypothesis.[25] Ha et al. detected a target appearance that had a higher hyperintensity in the center and a hypointense rim at the periphery, in hepatobiliary phase obtained by gadoxetic acid-MRI in breast cancer metastases and indicated that the relative contrast formed in the center resulted from desmoplastic reaction.[26] In our study, target sign could not be compared with histopathological sections since there were not histopathological sections obtained from metastases; however, in support of the hypotheses of Granata et al., Min et al., and Gourtsoyianni et al., we also think that hypointensity in the center detected in DWI is caused by a necrosis-related diffusion increase, and the hyperintense area at the periphery indicates a diffusion restriction caused by cellular intensity; central hyperintensity and peripheral hypointensity observed in all lesions with a target sign in ADC support this hypothesis.[19,21,25,27]

Another sign in our study is that metastases have lower ADC values compared with HCC. In the literature, there are several studies investigating ADC values of focal liver masses.[9-19] In these studies, ADC values in benign lesions were found to be higher than those of malignant lesions.[9-19] However, there are overlaps of ADC values in both benign and malignant lesions.[5,9,10,28] Therefore, the ADC value alone is not enough to characterize the lesion; morphological changes detected in DWI should also be taken into consideration. In the literature, ADC values of metastases range from 0.94 to 2.87.[29] The reason for this wide range may be the application of different DWI sequence parameters such as different b values and use or non-use of a parallel imaging technique.[15] In our study, we used a high b value, and as a result of this, we found an average ADC value for metastases close to the lower limit in the literature. In a large number of studies, ADC values of metastases were found to be lower than those of HCC,[9,10,13,14,18,19] while ADC values of metastases were found to be higher than those of HCC in several other studies.

[11,12,16,17] However, the difference between two groups was not statistically significant in these studies.[9,12,14,16,18] In our study, we found that ADC values in the metastasis group were lower than those of the HCC group; this difference was statistically significant.

In the literature, evaluation of focal liver masses with ROC curve is present in several studies; cut-off ADC values were used in distinguishing benign and malignant liver masses in several studies.[9,14-19] ADC values obtained by ROC analysis to distinguish metastatic liver lesions from HCC were determined in our study for the first time.

There are several limitations of our study. First, due to small number of patients, the statistical power the study has limited. Second, DWI-target sign was evaluated in metastases and HCC since these are the most frequent liver masses; other liver masses were not included in the study. In future studies, DWI-target sign in a larger series containing a higher number of liver masses should be performed. Moreover, DWI-target sign and contrast-enhanced MRI series should be compared to investigate whether there is an association between hypervascular or hypovascular liver lesions and target sign on DWI.

CONCLUSIONS

The target sign detected by DWI and ADC values can be used as MRI markers that enhance diagnostic accuracy in distinguishing the most frequent liver masses, metastatic liver lesions and HCC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Investigations Ethics Committee of Tokat Gaziosmanpaşa University Medical Faculty (21.12.2020 /16-KAEK-057).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Effect of Breastfeeding on the Risk of Developing Inflammatory Bowel Disease

Anne Sütü ile Beslenmenin İnflamatuar Bağırsak Hastalığı Gelişme Riski Üzerine Etkisi

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Abstract

Aim: This study aimed to investigate whether breastfeeding in early childhood affect the risk of devoloping inflammatory bowel disease (IBD).

Material and Method: The data of patients obtained from the survey were compared to the data of their non-IBD siblings as a control group. The relationship between the demographic and clinical chararecteristics of IBD patients and breastfeeding was also analyzed.

Results: 304 IBD patients were included in the study. 182 (59.9%) of the patients were diagnosed with ulcerative colitis (UC), and 122 (40.1%) with Crohn's disease (CD). The CD patients included in the study were compared to the CD siblings group of 332, and the UC patients compared with the UC siblings group of 508. Compared to the control groups, the proportion of those who never breastfed was higher in both the CD and UC groups (7.4% vs. 2.1% for CD [p=0.017] and 3.9% vs. 0.8% for UC [p=0.01]), and the risk of disease increased in those who was not breastfed (OR= 3.70 [1.35-10.16] for CD [p=0.017] and OR= 5.07 for UC [1.47-17.53] [p=0.010]). The protective effect against CD increased as the duration of breastfeeding increased, but that the protection increased with breastfeeding for up to 12 months for UC, and breastfeeding for more than 12 months did not provide additional protection. There was no relationship between breastfeeding and demographic and behavioral chracteristics of patients

Conclusions: Not having been breastfed in infancy increases the risk of developing both UC and CD, and as the duration of breastfeeding increases, the protection against diseases risk increases.

Keywords: Crohn's disease, ulcerative colitis, breastfeeding, disease risk

Öz

Amaç: Bu çalışmanın amacı, erken çocukluk döneminde anne sütü almanın inflamatuar bağırsak hastalığı (İBH) gelişme riskini etkileyip etkilemediğini araştırmaktır.

Gereç ve Yöntem: Anketten elde edilen hasta verileri İBH olmayan kardeşlerinden oluşan kontrol grubu ile karşılaştırıldı. Annesütü alma durumu ile İBH hastalarının demografik ve klinik özellikleri arasındaki ilişki de ayrıca analiz edildi.

Bulgular: Çalışmaya 304 İBH hastası dahil edildi. Hastaların 182'si (%59,9) ülsaratif kolit (ÜK), 122'si (%40,1) Crohn hastalığı (CH) tanılıydı. Çalışmaya dahil edilen Crohn hastalarının verileri 332 kişilik CH kardeş grubu ile ve ÜK hastalarının verileri de 508 kişilik ÜK kardeş grubunun verileri ile karşılaştırıldı. Hiç anne sütü almayanların oranı hem CH hem de ÜK grubunda, kontrol grubuna göre anlamlı olarak daha yüksekti (CH için %7,4 ve %2,1 [p=0,017] ve ÜK için %3,9 ve %0,8 [p=0,010]) ve hiç anne sütü almayanlarda hastalık riski anlamlı olarak artmıştı (CH için OR= 3,70 [1,35-10,16] [p=0,017] ve ÜK için OR= 5,07 [1,47-17,53] [p=0,010]). Ayrıca anne sütü alma süresi arttıkça CH'a karşı koruyucu etkinin arttığı, ÜK için ise 12 aya kadar emzirme ile koruyucu etkinin arttığı, ancak12 aydan fazla anne sütü almanın ek koruma sağlamadığı belirlendi. Anne sütü alma ile hastaların demografik ve klinik özellikleri arasında ilişki saptanmadı.

Sonuç: Bebeklik döneminde anne sütü almamış olanlarda hem ÜK hem de CH gelişme riski artmakta ve emzirme süresi arttıkça hastalık riskinden koruyuculuk artmaktadır.

Anahtar Kelimeler: Crohn hastalığı, Ülseratif kolit, anne sütü, hastalık riski

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INTRODUCTION

Although the etiology of Crohn's disease (CD) and ulcerative colitis (UC), which are chronic inflammatory diseases of the gastrointestinal tract, is still not fully understood, genetic predisposition, environmental causes and abnormal immune response against intestinal flora are the main suggested causes. Mutations in more than 200 genes that affect immune regulation functions in IBD have been identified.[1] However, in a study conducted with monozygotic twins, an association of up to 55% for CD and 17% for UC was found.[2] This indicates that genetic predisposition alone is not effective in the pathogenesis of the disease.

Many environmental factors that increase or decrease the risk of disease have been defined in patients with IBD, such as smoking, use of antibiotics and some other drugs, breast milk, excessive hygiene, past infections, deficiencies of some vitamins, and physical activity.[3] In patients with genetic predisposition, chronic inflammation develops in the intestines as a result of an excessive immune response to abnormal intestinal flora triggered by environmental factors.[4] It is known that the decrease in species such as *Bifidobacterium*, *Clostridium*, *Lachnospiraceae* and the increase in species such as *Proteobacteria*, *E. Coli*, Fusobacterium in the intestinal flora play a role in the development of IBD by changing the innate immune response.[5] Breastfeeding not only provides protection against infections in infants, but also has important effects on the microbiome composition of the intestines and immune tolerance, and plays a protective role against atopic, allergic and autoimmune diseases.[6-9] It has been reported that human milk oligosaccharides (HMOs), which are abundant in breast milk, act as a prebiotic to increase the beneficial species, especially *Bifidobacterium*, in the intestinal flora, and to reduce harmful bacteria such as *Acinetobacter* and with its antibacterial effect.[10,11]

Studies investigating the effect of breast milk on the risk of IBD so far are quite heterogeneous. While breastfeeding was found to be protective against IBD in some of them, it was found to have no effect in others.[12-14] Identifying and eliminating the modifiable factors in the etiology of diseases is important for the prevention of diseases. In this study, we compared the breastfeeding status of IBD patients and their healthy siblings in order to minimize the effects of genetic and environmental factors.

MATERIAL AND METHOD

Patients diagnosed with inflammatory bowel disease monitored in the Gastroenterology clinic of our hospital were included in the study. After obtaining approval from the ethics committee of our hospital (No: E1-22-2744), the patients' gender, age at diagnosis, place of residence (village, town, city), disease subgroup (UC, CD), disease localization according to the Montreal Classification[15] and CD behavior (inflammatory, stricture, fistulization, perianal disease), medications used, steroid refractoriness or dependence, and history of surgery related to IBD were recorded. The data on the duration of breastfeeding of patients were obtained by face-to-face questionnaire, and, for their siblings, by contacting them and their mothers. Patients who were not known for how long they were breastfed and their siblings were excluded from the study. Only those who were known for how long they were breastfed were included in the study.

Statistical Analysis

IBM SPSS Statisticsfor Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. Descriptive statistics (frequency, mean and SD, median and minimum-maximum) were calculated. Categorical variables were summarized as percentages. Normality analysis of the data was evaluated via Kolmogorov-Smirnov and Shapiro-Wilk tests. In group comparisons, a parametric test (Student's t-test) was used for normally distributed continuous variables, where as a non-parametric test (Mann-Whitney U and Kruskal-Wallis) was used for non-normally distributed variables. A chi-squared test or Fisher's exact test (when chi-squared test assumptions do not hold due to low expected cell count) was used to compare categorical variables in different groups. In estimating the risk ratio of the duration of breastfeeding on the disease state; It was tested by calculating odds ratios adjusted with 95% confidence intervals. Spearman correlation coefficient was used to evaluate the relationship between breastfeeding and disease. Statistical significance was considered $p \leq 0.05$ with a confidence interval (CI) of 95%.

RESULTS

304 IBD patients were included in the study. Mean age was 44.53±12.26 years, 173 (56.9%) of the patients were male. 182 (59.9%) of the patients were diagnosed with UC, and 122 (40.1%) with CD. Demographic and clinical characteristics of patients CD and UC are shown in **Table 1**. The data of a total of 840 siblings of these patients (508 siblings of UC patients and 332 siblings of CD patients) were analyzed. The data of 122 CD patients included in the study were compared to the CD siblings group of 332, and the data of UC patients with the UC siblings group of 508.

Comparing the 122 CD patients to 332 siblings, it was found that the rate of those who were not breastfed in the CD group was statistically significantly higher than the sibling group (7.4% and 2.1%, p=0.017) and the risk of disease increased significantly in those who were not breastfed (p=0.01, OR= 3.70 [1.35-10.16]). In addition, when the breastfed group was analyzed separately as >3 months, >6 months and >12 months, it was found that the protective effect increased as the duration increased (**Table 2**).

Table 1. Demographic and clinical characteristics of patients with Chron's disease and ulcerative colitis.

Demographic and clinical characteristics	CD (n=122)	UC (n=182)
Age	41.16±11.26 (17-82)	46.89±12.44 (18-76)
Gender		
Female	56 (45.9%)	75 (41.2%)
Male	66 (54.1%)	107 (58.8%)
Age at Diagnosis*	17-62 (34.08±9.97)	12-66 (38.22±12.07)
A1 (0-16 years)	0 (0.0%)	7 (3.9%)
A2 (17-40 years old)	93 (76.2)	97 (53.6%)
A3 (>40 years)	29 (23.8)	78 (42.5%)
UC localization*		
Proctitis (E1)	-	41 (22.5%)
Left Type (E2)		106 (58.3%)
Extensive (E3)		35 (19.2%)
CD localization*		
Ileal (L1)	51 (41.8%)	
Column (L2)	16 (13.1%)	-
ileocolon (L3)	55 (45.1%)	
Isolated upper GIS (L4)	0 (0.0%)	
CD behavior*		
Inflammatory (B1)	68 (55.7%)	
Stricturan (B2)	34 (27.9%)	-
Penetrating (B3)	20 (16.4%)	
Perianal disease (p)	21 (17.2%)	
IBD-related operation		
Yes	42 (34.4%)	13 (7.1%)
No	80 (55.6%)	169 (92.9%)
Steroid refractory/dependent		
No	83 (68.0%)	168 (92.3%)
Refractory	26 (21.3%)	9(4.9%)
dependant	13 (10.7%)	5 (2.8%)
Family history of İBD		
Yes	11 (9.0%)	33 (18.1%)
No	111 (91.0)	149 (81.9%)
Place of residence		
Village	7 (5.7%)	24 (13.2%)
Town	36 (29.5%)	43 (23.7%)
City	79 (64.8%)	115 (38.1%)
Patients' mean breastfeeding duration	12.92±9.47 (0-48 ay)	14.83±8.63 (0-36 ay)
Patients who have never been breastfed	9 (7.4%)	7 (3.9%)
Number of siblings	332 (Median:4 [0-9])	508 (Median:4 [0-18])
Siblings' mean duration of breastfeeding	15.51± 7.87 (0-48 ay)	14.67±7.06 (0-54 ay)
Siblings who have never been breastfed	7 (2.1%)	4 (0.8%)

CH: Crohn's disease, UC: ulcerative colitis, IBD: inflammatory bowel disease, *Montreal Classification

Table 2. Comparison of patients with Crohn's disease and their siblings in terms of duration of breast milk intake.

Breast milk intake	Patients n (%)	Sibling n (%)	p	Odds Ratio	95% Confidence Interval
No	9	7	0,017	3.7	1.346-10.159
Yes	113	325			
≤3 month	19	20	0,001	2.88	1.478-5.602
>3 month	103	312			
≤ 6 month	38	46	0,000	2.81	1.717- 4.608
>6 month	84	286			
≤12 month	77	161	0,006	1.87	1.187-2.283
>12	45	171			

Comparing the 182 UC patients to 508 siblings, the proportion of those with UC who were not breastfed was significantly higher than the sibling group (3.9% vs. 0.8%, p=0.010), and the risk of disease was found to be significantly increased in those who were not breastfed (OR=5.07 [1.47-17.53]). In addition, when the breastfed group was analyzed separately as >3 months, >6 months and >12 months, it was found that the protective effect increased as the duration increased (p<0.05), but there was no additional protection after 12 months (p>0.05) (**Table 3**).

Table 3. Comparison of patients with ulcerative colitis and their siblings in terms of duration of breast milk intake.

Breast milk intake	Patients n (%)	Sibling n (%)	p	Odds Ratio	95% Confidence Interval
No	7	4	0.01	5.07	1.466-17.525
Yes	175	504			
≤3 month	15	21	0.03	2.1	1.056-4.160
>3 month	167	487			
≤ 6 month	36	63	0.01	1.75	1.118-2.751
>6 month	146	445			
≤12 month	102	298	0.59	0.9	0.64-1.282
>12	80	210			

There was no relationship between the status and duration of breastfeeding and gender, age at diagnosis, place of residence, UC localization, operation history, medications used, and steroid refractoriness or steroid dependence in patients with UC.

Again, no relationship was found between the status and duration of breastfeeding and gender, age at diagnosis, place of residence, CD localization, CD behavior, perianal disease, operation history, medications used, and steroid addiction and refractoriness in patients with CD.

DISCUSSION

Many environmental factors along with genetic predisposition are blamed in the etiology of IBD, and the immune response against abnormal intestinal flora is mostly emphasized.[5] It has been reported that breast milk intake in the first period of life contributes to the formation of favorable intestinal flora and immunity.[10]

In a study conducted by the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) Group, they showed that breast milk is protective against IBD.[16] Similarly, in a meta-analysis of 35 studies by Xu et al.[13] it was found that the risk of both UC and CD was lower in those who received any amount of breast milk compared to those who did not receive any breast milk, and this effect was clearer in Asian populations than in European populations. In another meta-analysis, breast milk was found to be associated with a lower risk of CD and UC, while this relationship was found to be strong in studies with high methodological quality.[17] Contrary to these studies, it was reported that no relationship was found between breast milk and the risk of UC and CD in a prospective study including 146,681 women

in the National Health Survey I and II cohorts published in 2013.[14] Again, in different studies investigating the protectiveness of breast milk in patients with CD and UC, the effectiveness of breast milk could not be demonstrated.[18-21] Interestingly, Baron et al.[22] found that breast milk intake increased the risk of CD in their study in pediatric population. In our study, however, we found that having never been breastfed significantly increased the risk of developing both UC and CD, and even when the duration of breastfeeding was compared, the highest risk increase was seen in those who were never breastfed. Since siblings of the patients were taken as the control group in our study, the effect of genetic and environmental factors was minimized, and the effectiveness of breast milk was demonstrated. Considering the previous studies on colostrum, which is the milk secreted in the first days after birth, which reported that colostrum increases immunity, provides protection against harmful pathogens, and helps the development of the newborn immune system, this was thought to be no surprise.[23-25] We think that the reason why only less than 5% of the patients in our study were not breastfed, and that the rate of not receiving breast milk at all in studies in other countries was more than 20%[18-21] is due to the different patient populations studied, environmental factors and differences in local nutritional behaviors.

In addition to the protective effect of breast milk in CD and UC, the protective effect of the duration of breastfeeding against the disease has been investigated in different studies. In a meta-analysis, it was reported that the protective effect increased as the duration of breastfeeding increased.[13] Similarly, in another study, it was reported that the protective effect was clearer in those who were breastfed for longer than 12 months.[16] Ko et al.[26] analyzed separately the immigrants from the Middle East to Australia and the native Caucasian race and reported that having been breastfed for more than 3 months reduces the probability of developing CD, and that having been breastfed for more than 6 months reduces the likelihood of developing UC. In other studies, it has been reported that having been breastfed for more than 6 months reduces the risk of CD and UC.[27-29] Gearry et al.[30] on the other hand, reported that it is necessary to have been breastfed for at least 3 months for a protective effect. Differently, Sonntag et al.[18] found no significant difference in terms of breastfeeding duration in both CD and UC groups, while Striscioglio et al.[31] claimed that having been breastfed for longer than 3 months increases the risk of CD in their study on pediatric patients. In our study, we found that the protective effect of breast milk starts from the first months and the protective effect increases in parallel with long-term breastfeeding, however, having been breastfed for more than 12 months does not provide additional protection in UC patients. We think that different results may be caused by diet, medications used in childhood, immunization, environmental factors and variability in different populations in the etiology of the disease.

Siblings of the patients were taken as the control group in order to reduce environmental and genetic effects, and the main limitations of this study are that it is a study conducted with the questionnaire and where the information was questioned retrospectively, and that the smoking status of the patients and their siblings, the time of supplementary food initiation, diet, childhood infections, vaccination, and hygiene conditions that may be associated with the risk of disease are not known.

CONCLUSION

Not having been breastfed in infancy increases the risk of developing both CD and UC, the protective effect of breast milk starts from the first months and the protective effectiveness increases in parallel with long-term breastfeeding.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 29/06/2022, Decision No: E1-22-2744).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

A Quasi-experimental Intervention Study on Handwashing Behavior of Healthcare Workers in the Emergency Department

Acil Serviste Görev Yapan Sağlık Çalışanlarında El Yıkama Davranışı Hakkında Yarı Deneysel Bir Çalışma

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Abstract

Aim: In this study, it was aimed to determine the attitudes, behaviors and knowledge of healthcare workers working in the emergency department of a hospital and to ensure correct handwashing with an intervention related to handwashing behavior.

Material and Method: The research was a quasi-experimental intervention study (retrospective pre-test/post-test design). The number of participants was 131 (research participation rate 86.7%). A data collection form comprising 37 questions was used. As a training intervention, a text was read to the participants under observation. Data were summarized with mean±standard deviation, median (min-max), frequency distributions, and percentages. The chi-square and Mc-Nemar tests were applied to investigate the relationships between data. $p<0.05$ was considered significant.

Results: The mean age of the participants was 32.04±6.52, 51.5% were women and 74.8% were nurses. Those who thought that they washed their hands adequately during an 8-hour work period were 67.2%. 69.5% of the healthcare workers answered correctly to 70% and more of the knowledge questions and got a score of 9 and above. A significant difference was found in 10 of the 14 intervention questions regarding handwashing ($p<0.05$).

Conclusion: In the research, it is found that the rate of those who think that they wash their hands enough during an 8-hour work period is more than two-thirds, found that more than two-thirds of the participants gave correct answers to the knowledge level questions related to handwashing and found that the training intervention performed is effective.

Keywords: Handwashing, healthcare worker, emergency service, training

Öz

Amaç: Bu çalışmada bir hastanenin acil servisinde görev yapan sağlık çalışanlarının el yıkama ile ilgili tutum, davranış ve bilgilerini değerlendirmek ve el yıkama davranışıyla ilgili bir müdahaleyle doğru el yıkamalarını sağlamak amaçlanmıştır.

Gereç ve Yöntem: Araştırma yarı deneysel bir müdahale çalışmasıdır (retrospektif ön-test/son-test tasarımı). Katılımcı sayısı 131'dir (araştırmaya katılma oranı %86,7). Araştırmada 37 sorudan oluşan bir veri toplama formu kullanılmıştır. Eğitim müdahalesi olarak katılımcılara gözlem altında bir metin okutulmuştur. Veriler ortalama±standart sapma, ortanca (min-maks), frekans dağılımları ve yüzdelikler ile özetlenmiştir. Veriler arası ilişkilerin araştırılmasında ki-kare ve Mc-Nemar testleri uygulanmıştır. $p<0,05$ anlamlı kabul edilmiştir.

Bulgular: Katılımcıların yaş ortalaması 32,04±6,52, %51,5'i kadın ve %74,8'i hemşireydi. Sekiz saatlik bir iş periyodunda ellerini yeterli sayıda yıkadığını düşünenler katılımcıların %67,2'siydi. Sağlık çalışanlarının %69,5'i bilgi sorularının %70'ine ve daha fazlasına doğru yanıt vererek 9 ve üzerinde bir puan aldı. El yıkamaya ilişkin 14 müdahale sorusundan 10'unda istatistiksel açıdan anlamlı fark bulundu ($p<0,05$).

Sonuç: Araştırma sonucunda sekiz saatlik bir iş periyodunda ellerini yeterli sayıda yıkadığını düşünenlerin oranının katılımcıların üçte ikisinden fazla olduğu, el yıkamayla ilişkili bilgi düzeyi sorularına katılımcıların üçte ikisinden fazlasının doğru yanıt verdiği ve yapılan eğitim müdahalesinin etkili olduğu bulunmuştur.

Anahtar Kelimeler: El yıkama, sağlık çalışanı, acil servis, eğitim

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INTRODUCTION

It is a historical fact known since the time of Ignaz Semmelweis (1818-1865) that it is important on hand hygiene both in daily life and in the working environment.[1] The lack of compliance with hand hygiene in numerous sectors, particularly in the fields of health-related work, can ease the spread of infectious diseases. Because of low hand hygiene compliance in healthcare workers (HCWs), healthcare-associated infections caused by highly virulent and multi-drug-resistant microorganism species may occur.[2] Every year, lots of patients worldwide are affected by healthcare-associated infections. However, the true global burden of healthcare-associated infections is unknown because of the difficulty of collecting reliable data in this area.[3] In a systematic review/meta-analysis study conducted by the World Health Organization (WHO), including studies on healthcare-associated infections from 23 high-income countries (131 national and multicenter studies) covering the years 1995-2010, the frequency of healthcare-associated infections was found 7.6% (3.5%-12%).[4] The Centers for Disease Control and Prevention (CDC) reports that one out of every 31 patients admitted to the hospital develops a healthcare-associated infection.[5]

Unclean hands of HCWs are held responsible for 20-40% of healthcare-associated infections, which cause serious morbidity, mortality, and cost increase. Up to 50% of healthcare-associated infections can be prevented with hand hygiene improvement programs.[2,3,6] WHO has in simple terms identified five key moments of hand hygiene. Accordingly, hand hygiene should be provided before contact with the patient, before aseptic procedures, after contact with the patient, after contact with body fluids, and after contact with surfaces around the patient.[6]

In the 2009 report of the WHO, it was reported that compliance with hand hygiene in HCWs was 38.7% (5%-89%) on average.[6] The CDC (2019) states that HCWs wash only half of the time they need to wash their hands while they work.[5] In a systematic review study covering the years 2014-2020, the compliance rate of HCWs with hand hygiene was found to be 41%.[7]

In this study, it was aimed to determine the attitudes, behaviors and knowledge of HCWs working in the emergency department about handwashing and to ensure correct handwashing with an intervention related to handwashing behavior.

MATERIAL AND METHOD

This research is a quasi-experimental type of intervention study. Ethical permission (Date: 28.04.2017 Number: 2017/904) from Necmettin Erbakan University Meram Faculty of Medicine Ethics Committee and institutional permission from Konya Provincial Health Directorate were obtained. The research was carried out in the emergency department of a training and research hospital in Konya province Meram district.

The population of the research comprised 151 physicians and nurses working in the emergency department between December 1, 2019 and January 31, 2020. Sample selection was not made for the research, and it was aimed at reaching the entire population. A total of 20 physicians and nurses did not participate in the study because of reasons such as not wanting to participate in the study, being on maternity leave, or being on assignment. The number of participants was 131 (research participation rate 86.7%).

A data collection form comprising 37 questions and 3 main parts was applied in the research. In the first part, some sociodemographic characteristics of the participants (6 questions), and in the second part, their knowledge, attitudes, and behaviors about handwashing were questioned (17 questions). In the third and last part, a text about handwashing (**Table 1**) was read to the participants under observation. It was thought that it would be a more effective method to take people one-on-one and explain to them the rights and wrongs of hand washing through a text by eliminating environmental distractions, rather than a training and intervention by gathering a group of people in a hall with many distractions and reading and explaining something from a slide for a certain period of time. Participants were asked to evaluate the knowledge and practices in the text they read, and whether they knew the text before reading it, by answering the 14 questions in the last part. This was a retrospective pre-test/post-test design.[8] The second part was the pre-test and the third part was the post-test. Within the research, a score was calculated from the knowledge questions. The lowest score that can be obtained from knowledge questions is 0, and the highest score is 12. Answering at least 70% of the knowledge questions correctly was evaluated as 'having sufficient knowledge'. In calculating the score, the 70% value was determined by the researchers with a generally accepted preconception.

Table 1. The text read to HCWs about handwashing

Handwashing is the simplest and most effective method of preventing healthcare-associated infections. Handwashing is of three types: Social handwashing, hygienic handwashing and surgical handwashing. A HCW working in a clinic is expected to know and practice hygienic handwashing. Hygienic handwashing is washing the palms, dorsum of the hands, wrists and interdigitals with warm water and soap for at least 15 seconds. Hot and cold waters are not recommended, as they will increase the risk of dermatitis. The area where the most intense microorganism is found on the hands is between the fingers. During handwashing, the faucet should not be touched and the faucet should be opened and closed with the help of paper towels. After handwashing, hands should be dried with a paper towel. Hands can be washed using liquid soap, foam soap, chlorhexidine soap, povidone iodine soap, chlorhexidine alcohol solution, povidone iodine alcohol solution. Using solid soap should be avoided. There are two types of flora on the hands, transient and resident. Microorganisms that are transmitted from patients to the hands of healthcare workers and adhere to the hand superficially constitute the transient flora. Transient flora has been associated with healthcare-associated infections. It is aimed at cleaning the transient flora with handwashing. According to the five moments of hand hygiene of WHO, hands should be washed in the following situations: 1-Before contact with each patient, 2-After contact with each patient, 3-After contact with body fluids, 4-Before aseptic procedures (such as oral care, wound care, catheter insertion), 5-After contact with surfaces around the patient.

The participants were informed and, after their verbal consent was obtained, the data collection form was applied under observation. The same researcher collected the data from all participants during the HCWs' lunch break. The data collection process was tried to be standardized by this application. The steps during the application of the data collection form are shown in **Figure 1**.

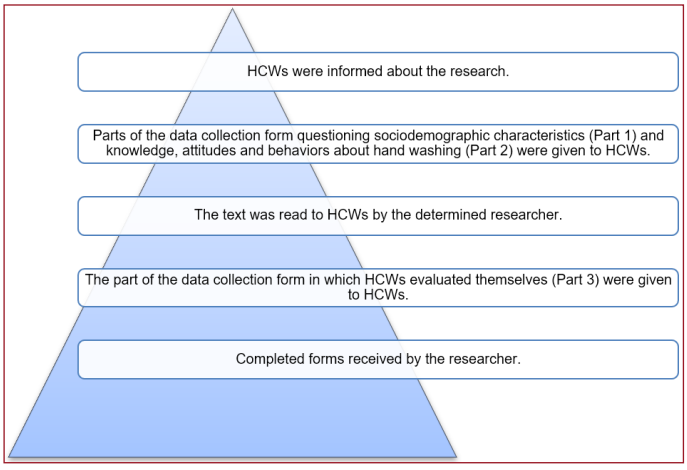

Figure 1. The steps during the application of the data collection form

Statistical Analysis

Data entry and analysis were performed with Jamovi software version 2.3. Data were summarized with mean±standard deviation, median (min-max), frequency distributions, and percentiles. The chi-square and Mc-Nemar tests were used to investigate the relationships between the data. $p<0.05$ was considered statistically significant.

RESULTS

Sociodemographic Characteristics

The mean age of 131 people participating in the study was 32.04±6.52. 51.5% of the HCWs were women and 48.5% were men. Sociodemographic characteristics of the HCWs are shown in **Table 2**.

Table 2. HCWs' sociodemografic characteristics

Characteristics	
Age (year)	34.78±6.57 (min:24, max:55)
Sex	
Female	51.5% (n=67)
Male	48.5% (n=63)
Marital status	
Single	39.7% (n=52)
Married	60.3% (n=79)
Educational status	
High school	14.5% (n=19)
University (2 years)	19.1% (n=25)
University (4 years)	66.4% (n=87)
Profession	
Phsyician	25.2% (n=33)
Nurse	74.8% (n=98)
Total working time (year)	8.90±6.32

Handwashing Characteristics

The rate of participants who received training on handwashing during school years was 89.2%, and the rate of participants who received training on handwashing in working life was 93.8%. The characteristics of healthcare workers related to handwashing are shown in **Table 3**.

Table 3. HCWs' handwashing characteristics

Characteristics	n	%
Receiving training on handwashing during school years		
Yes	116	89.2
No	14	10.8
Receiving training on handwashing in working life		
Yes	122	93.8
No	8	6.2
Thinking that he/she wash his/her hands enough during an 8-hour work period		
Yes	88	67.2
No	43	32.8
The reason that reduces the frequency of handwashing the most		
Workload	66	51.6
Damage to hands due to washing	35	27.3
Lack of washbasin	3	2.3
Distrust of handwashing environment and material	14	10.9
Other	10	7.8
The most frequently used material for handwashing		
Antiseptic solution	15	11.6
Liquid soap	110	85.3
Water only	2	1.6
Other	2	1.6

The mean number of handwashing was 16.50±10.45 and the median number of handwashing was 15 (1-50) during an eight-hour work period. Of those who thought that they washed their hands adequately during an 8-hour work period (n=88), 17% were physicians, and 83% were nurses.

Level of Knowledge Related to Handwashing

61.2% of the HCWs knew that the most effective method of preventing nosocomial infections was handwashing. The rate of those who knew that the flora responsible for hospital infections was transient flora was 76%. 61.1% of the HCWs knew exactly and accurately the situations where hands should be washed according to the five moments of hand hygiene of WHO. The knowledge levels of the HCWs regarding hand hygiene are shown in **Table 4**.

69.5% of the HCWs answered 70% or more of the knowledge questions correctly and scored 9 or more. There was a significant difference between responding to 70% or more of the knowledge questions and gender (Chi-square=7,879, $p=0.005$). The frequency of females who scored 9 and above was higher than that of males. There was no relationship between the variables of marital status, education level, occupation, handwashing education at school, handwashing education in working life, and thinking that he washed his hands adequately ($p>0.05$).

Table 4. Knowledge levels of HCWs about hand hygiene

Questions	n	%
What is the most effective way to prevent hospital infections?		
Using personal protective equipment	45	34.9
Handwashing*	79	61.2
Other	5	3.9
Which flora is implicated in healthcare associated infections?		
Resident flora	29	24.0
Transient flora*	92	76.0
Which region has the most microorganisms on the hand?		
Palm	24	18.5
Dorsum of the hands	0	0.0
Interdigital*	64	49.2
Fingertips	33	25.4
Wrist	2	1.5
Other	7	5.4
Is it enough to wash hands only with water?		
Yes	7	5.3
No*	124	94.7
Should hands be dried after washing?		
Yes*	119	91.5
No	11	8.5
Should hands be washed after wearing gloves?		
Yes*	118	92.2
No	10	7.8
Should hands be washed before contact with each patient?		
Yes*	114	87.7
No	16	12.3
Should hands be washed after contact with each patient?		
Yes*	126	96.9
No	4	3.1
Should hands be washed after contact with body fluids?		
Yes*	112	86.2
No	18	13.8
Should hands be washed before aseptic procedures?		
Yes*	100	76.9
No	30	23.1
Should hands be washed after contact with surfaces around the patient?		
Yes*	95	73.1
No	35	26.9
How long should the hygienic handwashing period be?		
10 seconds	15	11.4
15 seconds*	30	22.9
30 seconds	79	60.3
Other	7	5.3
Total score [mean±sd/median(min-max)]	9.14±1.62 / 9 (4-12)	
Total score for physicians	9.10±1.95 / 9 (4-12)	
Total score for nurses	9.16±1.50 / 9 (5-12)	

*Indicates correct answers.

Handwashing-Related Intervention Results

After reading the text containing information about handwashing (**Table 1**), the participants were asked to state what they knew as "I knew" and what they did not know as "I didn't know" before reading this text. HCWs evaluated themselves by this method. According to this, it was determined that the HCWs have already known the information 'Handwashing is the most effective and simplest method to prevent healthcare-associated infections', 'Hands should be washed after contact with each patient', 'Hands should be washed after contact with body fluids' and 'Before aseptic procedures (such as oral care, wound care, catheters) hands should be washed'. The knowledge questions answered before reading the text (pre-test) and I knew/I didn't know answers that HCWs evaluated themselves (post-test) were analyzed with the Mc-Nemar test. The results of the intervention are shown in **Table 5**.

Table 5. Handwashing intervention results

Expressions	p
Handwashing is the simplest and most effective method of preventing healthcare-associated infections.	0.125
Handwashing is of three types: Social handwashing, hygienic handwashing and surgical handwashing.	0.001*
A HCW working in a clinic is expected to know and practice hygienic handwashing.	0.016*
Hygienic handwashing is washing the palms, dorsum of the hands, wrists and interdigitals with warm water and soap for at least 15 seconds.	0.001*
After handwashing, hands should be dried with a paper towel.	0.001*
Hands can be washed using liquid soap, foam soap, chlorhexidine soap, povidone iodine soap, chlorhexidine alcohol solution, povidone iodine alcohol solution.	0.001*
There are two types of flora on the hands, transient and resident.	0.001*
Transient flora has been associated with healthcare-associated infections.	0.001*
It is aimed at cleaning the transient flora with handwashing.	0.001*
Hands should be washed before contacting each patient.	0.031*
Hands should be washed after contact with each patient.	0.500
Hands should be washed after contact with body fluids.	1.000
Hands should be washed before aseptic procedures (such as oral care, wound care, catheter insertion).	0.250
Hands should be washed after contact with surfaces around the patient.	0.001*

*The ones with statistically significant difference between the pre-test and post-test are marked.

DISCUSSION

The rate of participants who think that they wash their hands adequately in an eight-hour work period is 67.2%. Of those who thought that they washed their hands adequately during an 8-hour work period, 17% were physicians and 83% were nurses. In the study by Yurttas et al.[9] the hand hygiene compliance of the participants was 66.4% among physicians and 73.9% among nurses-midwives. In the study by Dikis et al.[10] in which they evaluated 5 years from 2014 to 2018, hand hygiene compliance rates were found between 37% and 70% in nurses and between 28% and 49% in physicians. In the study by Kosucu et al.[11] the general hand hygiene compliance rate of HCWs was found to be 58%, nurses 69%, and physicians 45%. In the systematic review by Gon et al.[12] in which they included 15 studies, hand hygiene compliance among birth attendants working in health institutions are in a wide range, from 0% to 100%. Phan et al.[13] observed that hand hygiene compliance was 43.6% and increased after the intervention. The rates of compliance with hand hygiene in

different institutions evaluated in the study by Tyagi et al. were found to be 12%, 33%, and 44%.[14] Studies evaluating handwashing compliance with a survey method similar to our study could not be found in the literature by researchers. For this reason, studies that evaluated handwashing compliance by observation were included in the discussion. The handwashing rate we found in our research is consistent with the literature. It has also been known for years that nurses wash their hands at a higher rate than physicians do. The reason for this may be that nurses take more roles in patient care-related jobs compared to physicians.

In our study, HCWs stated work intensity as the reason that reduces the frequency of hand washing the most. In a study by Aktug Demir et al.[15] in another hospital in Konya, it was found that the reason that most decreased the frequency of handwashing was workload. In the WHO's Hand Hygiene Guide in Healthcare, irritation caused by hand hygiene products, lack of placement of hand hygiene products, lack of materials, workload, lack of time, thinking that the patient's needs are more priority, thinking that the risk of infection transmission from patients is low, belief that wearing gloves is sufficient for hygiene, lack of knowledge, lack of role models and forgetfulness are stated as the reasons that reduce handwashing compliance rates.[6]

It was found that 61.1% of the research participants knew exactly and correctly the situations in which hands should be washed according to the five moments of hand hygiene of WHO. In the study by Aktug Demir et al., the rate of those who fully knew the five moments of hand hygiene was 10%.[16] In the study by Toraman et al., handwashing rates were reported as 70% before contact with the patient and 81% after contact with body fluids.[17] In the study by Kosucu et al., based on the five moments of hand hygiene, the compliance of HCWs was found to be 58%.[11] In the literature, there are different rates of knowing and complying with the five moments of hand hygiene. The reason for this situation may be the variations of the groups included in the research, as well as the hand hygiene-related training and the content of the training received.

69.5% of the participants provided correct answers to at least 70% of the knowledge level questions related to handwashing. There was no significant difference between physicians and nurses in terms of hand hygiene knowledge level. In the study by Ozturk et al., the mean level of knowledge evaluated with 10 questions was 8.[18] In the study by Aktug Demir et al., the rate of correct answers to the 11 questions asked to evaluate the level of hand hygiene knowledge was between 46.2% and 94.6%.[15] The situation we determined in our study and the scores and rates in the literature are similar. It can be stated that the level of knowledge about hand washing of the HCWs within the research is at a moderate level. The reason for this situation may be handwashing training and the content of the training. However, it is thought that these rates may have increased due to the effect of the COVID-19 pandemic.

In the self-evaluation section, most participants stated that they did not know 10 of the 14 statements before the research. In the study by Ozturk et al.[18] the mean level of knowledge evaluated with 10 questions was found to be 8 before the education and 9 after the education. Wisniewski et al.[19] determined that the educational intervention related to hand hygiene had positive results on HCWs. In the study by Karaoglu and Akın,[20] it was found that the knowledge scores of nurses increased after the training. Since the studies in which the pre-test and post-test application were made consecutively could not be reached by the researchers, the studies that had time between the pre-test and post-test application were used in the discussion. Both in our study and similar studies in the literature, the educational intervention provided an increase in the level of hand hygiene knowledge in HCWs. These increases can be associated with the need to remind the subject at regular intervals.

Advantages and Limitations of the Research

The research was carried out in the busiest emergency service in the city center. In this way, the status of the HCWs serving a large number of patients was evaluated. With the research, the attention of the HCWs was drawn to handwashing. Because of the intervention feature of the study, the employees were allowed to correct their deficiencies and mistakes. Additionally, since the research was conducted in the pre-covid-19 pandemic period, it is important to indicate the handwashing status of the HCWs in the pre-pandemic period. With this feature, it will be a good benchmark for similar studies to be conducted during and after the Covid-19 pandemic.

All emergency services, both public and private, in the province could not be included in the research due to time and cost constraints. Since the study is an intervention type, its generalizability to the population of the study is limited. In our research, a method in which individuals evaluate themselves was used (retrospective pre-test/post-test). No follow-up/observation was made. Sociodemographic characteristics such as age, gender, profession, and hand washing characteristics of 20 people who did not participate in the study are not known. These are the limitations of the study.

CONCLUSION

As a result of the research, it was determined that most HCWs received training on handwashing; they thought they washed their hands adequately; they knew the five moments of hand hygiene of WHO correctly, and the level of knowledge about handwashing was high. The educational intervention was effective. These rates may have increased because of the importance of hand hygiene messages widely presented from various sources during the Covid-19 pandemic.

It is thought that handwashing, which is a key factor in preventing the spread of communicable diseases and reducing healthcare-associated infections, should be added to the pre-graduate and post-graduate training programs of the HCWs at regular intervals, by determining the content, under observation and in practice. Additionally, conducting research on the knowledge levels of the HCWs before and after the training activities may play an important role in evaluating the training effectiveness and improving the training provided.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Necmettin Erbakan University Meram Faculty of Medicine Non-Pharmaceutical and Non-Medical Device Research Ethics Committee (Date: 28.04.2017, Number: 2017/904).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Use of Early Warning Scoring Systems to Predict the Prognosis of COVID-19 Patients in the Emergency Department

Acil Serviste COVID-19 Hastalarının Prognozunu Tahmin Etmek İçin Erken Uyarı Puanlama Sistemlerinin Kullanımı

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Abstract

Aim: Increased emergency department (ED) admissions and the need for intensive care unit (ICU) brought with the pandemic has led to the need to make fast and accurate decisions. Early warning scores (EWS) may be useful in ED in this regard. This study was performed to evaluate the effectiveness of EWS in predicting mortality and need for ICU of patients with COVID-19.

Material and Method: This retrospective observational study was performed with subjects presented to the ED and were later admitted to a general ward or to the ICU because of COVID-19. Subjects aged ≥18 years with positive RT-PCR were included in the study. Subjects experienced a cardiac or respiratory arrest or intubated at the time of presentation to the ED and pregnant women were excluded from the study. MEWS, NEWS, NEWS-2, REMS, and qSOFA scores were calculated using patients' data on first presentation. We examined the association of these scoring systems with mortality and need for ICU.

Results: While 60(10%) of the 600 patients participating in the study were admitted to the ICU, 222(37%) patients died. The scoring systems' negative predictive values for predicting ICU admission were 0.95, 0.98, 0.97, 0.96, and 0.96 respectively and for predicting mortality were 0.61, 0.67, 0.67, 0.66, and 0.61 respectively. All scorings assessed were significant predictors of the need for ICU and mortality in patients with COVID-19.

Conclusions: All evaluated scoring systems were successful; however, NEWS and NEWS-2 had the highest predictive value both for the need for ICU and mortality.

Keywords: Early warning score, Emergency medicine, COVID-19, prognosis, mortality

Öz

Amaç: Pandemi ile birlikte artan acil servis (AS) başvuruları ve yoğun bakım (YBÜ) ihtiyacı, hızlı ve doğru karar verme ihtiyacını doğurmuştur. Erken uyarı skorları (EUS) bu konuda acil serviste faydalı olabilir. Bu çalışma, EUS'nin COVID-19 hastalarının mortalitesini ve YBÜ ihtiyacını öngörmedeki etkinliğini değerlendirmek için yapıldı.

Gereç ve Yöntem: Bu retrospektif gözlemsel çalışma, acil servise sunulan ve daha sonra COVID-19 nedeniyle genel servise veya yoğun bakım ünitesine kabul edilen deneklerle gerçekleştirildi. Pozitif RT-PCR'si olan ≥18 yaşındaki denekler çalışmaya dahil edildi. Acil servise başvuru anında kalp veya solunum durması yaşayan veya entübe olan denekler ve hamile kadınlar çalışmadan çıkarıldı. MEWS, NEWS, NEWS-2, REMS ve qSOFA skorları hastaların ilk başvurudaki verileri kullanılarak hesaplandı. Bu skorlama sistemlerinin mortalite ve YBÜ ihtiyacı ile ilişkisini inceledik.

Bulgular: Çalışmaya katılan 600 hastanın 60'ı (10%) yoğun bakıma alınırken, 222 (37%) hasta öldü. Puanlama sistemlerinin YBÜ yatışını öngörmedeki negatif tahmin değerleri sırasıyla 0.95, 0.98, 0.97, 0.96 ve 0.96 ve mortaliteyi tahmin etmede sırasıyla 0.61, 0.67, 0.67, 0.66 ve 0.61 idi. Değerlendirilen tüm skorlar, COVID-19 hastalarında YBÜ ihtiyacı ve mortalitenin önemli belirleyicileriydi.

Sonuç: Değerlendirilen tüm puanlama sistemleri başarılıydı; ancak NEWS ve NEWS-2 hem YBÜ ihtiyacı hem de mortalite açısından en yüksek prediktif değere sahipti.

Anahtar Kelimeler: Erken uyarı skoru, Acil tıp, COVID-19, prognoz, mortalite

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INTRODUCTION

First identified in the city of Wuhan, China in December 2019, the novel coronavirus (SARS-CoV-2) has led to an outbreak of respiratory disease called coronavirus infectious disease 2019 (COVID-19), which has currently affected millions of people worldwide (1). COVID-19, with its several variants detected over time, typically presents with fever, myalgia, fatigue and dry cough, and some patients develop severe dyspnea and hypoxemia days after the onset of symptoms, resulting in more frequent presentation to emergency department (ED) and increased need for admission to general ward and intensive care unit (ICU) in hospitals (2). Previous studies have reported that the prevalence of hypoxemic respiratory failure is approximately 20% in hospitalized COVID-19 patients, and more than 25% of these patients require admission to ICU (3). In addition to simple laboratory parameters such as BUN/lymphocyte ratio (4), BUN/ albümin ratio (5), lactate clearance (6), various early warning scorings (EWS) (7) have been tried to predict the need for intensive care and mortality in COVID-19 patients.

EWS are physiological scoring systems based on prompt and quantitative evaluation of changes in vital symptoms (8). They have been initially developed to ensure early stabilization and transfer to the ICU when needed, to detect preventable cardiac arrests, to identify and monitor hospitalized patients at risk for deterioration outside critical care points (9,10). These scoring systems have also been investigated for their potential in identifying critically ill patients in the triage area (11), and the Rapid Emergency Medicine Score (REMS) has been specifically developed for this purpose (12). Although the National Early Warning Score (NEWS) (13) is the most common scoring system used in studies conducted with patients presenting to ED to predict both in-hospital mortality and ICU admissions (11). Furthermore, it is unclear which EWS is the most accurate for the triage of COVID-19 patients in the ED. Therefore, the primary objective of this study was to evaluate the potential utility of various EWS for triage in ED in Turkey which have been overstretched by COVID-19 cases.

MATERIAL AND METHOD

Study Design and Patient Selection

This is a retrospective, cross-sectional and observational study. After receiving approval from the local ethics committee with approval number of 0265 (27/05/2021), the study was conducted between 01/04/2020 and 01/04/2021 with patients who presented to the ED of a tertiary hospital with a preliminary diagnosis of COVID-19, who tested positive for PCR (regardless of variant) and who were admitted to the general ward or ICU at the same hospital. Patients aged <18 years at the time of presentation to the ED, patients who were intubated or had cardiac or respiratory arrest on presentation and pregnant patients were excluded from the study.

Data Collection

Data were collected retrospectively, by screening medical records of patients who presented to the ED of our hospital and were later admitted to a general ward and/or to the ICU with a preliminary diagnosis of PCR+COVID-19. Patients' data collected from screened files including respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse rate, temperature, 02 saturation, state of consciousness (GCS/AVPU), admission status (general ward/ICU), mortality, age, and sex were recorded in prepared case report forms. EWS were calculated for each patient using the recorded data. For this purpose, we used MEWS, NEWS, NEWS 2, qSOFA, and REMS early warning scoring systems, which are known to be valid and quick tools in ED settings. MEWS is a scoring scale consisting of systolic blood pressure, heart rate, respiratory rate, body temperature, and state of consciousness parameters and scored between 0 and 14. NEWS is a scoring scale consisting of the parameters of systolic blood pressure, respiratory rate, oxygen saturation, need for any suplemental oxygen, body temperature and state of consciousness and scored between 0 and 20. The NEWS-2 is a scoring scale consisting of systolic blood pressure, respiratory rate, oxygen saturation, presence of hypercapnia, need for oxygen therapy, body temperature, pulse rate, and state of consciousness and scored between 0 and 20. qSOFA is a scoring scale consisting of consciousness status, systolic blood pressure, respiratory rate parameters and scored between 0 and 3. REMS is a scoring scale consisting of age, mean arterial pressure, heart rate, respiratory rate, peripheral oxygen saturation, and state of consciousness, and scored between 0 and 26. Each scoring was calculated via a web-based calculator (www.mdcalc.com).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 26.0 for windows (IBM Corp., Armonk, New York, USA) statistical software suite. When evaluating variables according to the need for ICU; the independent samples t-test was used for age, respiratory rate, temperature, SBP, MAP, pulse rate, oxygen saturation, NEWS, NEWS-2, and REMS; and the Mann-Whitney U test was used for DBP, GCS, MEWS, qSOFA. Yates' Continuity Correction of the Chi-Squared test was used to examine the association between ICU admission status, sex and assisted ventilation, and Pearson's Chi-squared test was used to examine the association between ICU admission status and consciousness. In evaluating variables by mortality; the independent samples t-test was used for evaluating age, respiratory rate, SBP, DBP, MAP, pulse rate, oxygen saturation, NEWS and REMS, and the Mann-Whitney U test was used to evaluate temperature, GCS, MEWS, NEWS-2, and qSOFA. The association between mortality, sex, assisted ventilation, and consciousness was evaluated using Pearson's Chi-squared test. Statistical significance was set at $p<0.05$.

RESULTS

The patient flow chart, which shows inclusion and exclusion steps, is given in **Figure 1**. Among the 600 patients included, 365 (60.8%) were men and 235 (39.2%) were women. The mean age of the patients was 67.13±15.24 years. A total of 540 (90%) patients were admitted to the general ward and 60 (10%) were admitted to the ICU. Furthermore, 222 (37%) patients died and 378 (67%) patients were discharged. The characteristics of the sample and the breakdown of scores by patient outcome are provided in **Table 1**.

ROC analysis was performed to evaluate the value of MEWS, NEWS, NEWS-2, REMS, and qSOFA scoring systems in predicting the need for ICU admission in patients with COVID-19 (AUC:0.776, 0.778, 0.763, 0.758, and 0.724, respectively) (**Figure 2**). ROC analysis found a cut-off value of 2.5 for MEWS, 4.5 for NEWS, 4.5 for NEWS-2, 5.5 for REMS and 0.5 for qSOFA. The scoring systems' negative predictive values (NPV) at indicated specificity and sensitivity for predicting ICU admission were 0.95, 0.98, 0.97, 0.96, and 0.96 respectively, and were found to be statistically significant (p<0.001) (**Table 2**). When patients were divided into two groups as those at high and low risk for ICU admission according to the specified cut-off values, the high risk categorization for each scoring system was associated with ICU admission (p<0.001).

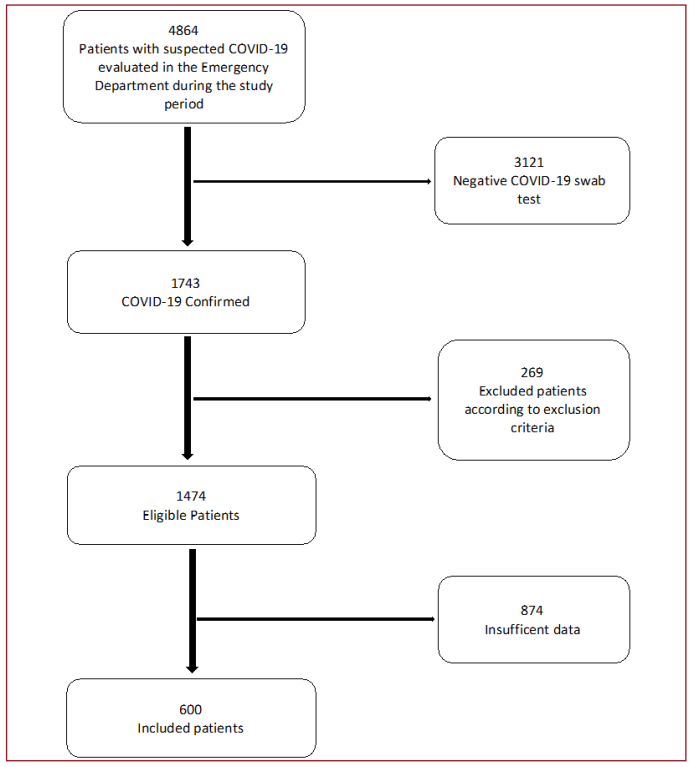

Figure 1. Patient flow chart

Table 1: Characteristics of the sample and breakdown of scores by patient outcome.

	All Patients (n=600)	Need for ICU			Mortality		
		No (n=540 [90%])	Yes (n=60 [10%])	P	Survived (n=378 [63%])	Dead (222 [37%])	P
Age (year)	67.13 ± 15.24	66.8 ± 15.47	70.17 ± 12.73	0.061+	65.45 ± 16.57	70 ± 12.18	<0.001+
Sex				0.780			0.993**
Male	365 (60.8)	327 (60.6)	38 (63.3)		230 (60.8)	135 (60.8)	
Female	235 (39.2)	213 (39.4)	22 (36.7)		148 (39.2)	87 (39.2)	
Respiratory rate	20.52 ± 5.38	19.74 ± 4.45	27.53 ± 7.6	<0.001+	19.78 ± 4.94	21.77 ± 5.87	<0.001+
Assisted ventilation				<0.001.			0.001**
No	247 (41.2)	235 (43.5)	12 (20)		175 (46.3)	72 (32.4)	
Yes	353 (58.8)	305 (56.5)	48 (80)		203 (53.7)	150 (67.6)	
Temperature	36.5 (36.1–36.8)	36.5 (36.1–36.8)	36.7 (36.1–37)	0.353*	36.5 (36.1–36.8)	36.5 (36.1–37)	0.236*
SBP	127.82 ± 21.39	127.25 ± 20.56	132.9 ± 27.47	0.127+	128.5 ± 20.7	126.65 ± 22.53	0.306+
DBP	71 (62–80)	72.5 (68–80)	70 (55–75)	0.372*	74.91 ± 13.81	73.46 ± 13.17	0.207+
MAP	92.18 ± 14.63	92.08 ± 14.25	93.1 ± 17.77	0.669+	92.77 ± 14.67	91.19 ± 14.53	0.203+
Pulse	90.31 ± 17.45	89.8 ± 16.71	94.9 ± 22.73	0.096+	89.31 ± 16.75	92.02 ± 18.5	0.066+
Consciousness				<0.001**			0.053**
Conscious	576 (96)	525 (97.2)	51 (85)		368 (97.4)	208 (93.7)	
Confused	19 (3.2)	14 (2.6)	5 (8.3)		7 (1.9)	12 (5.4)	
Unconscious	5 (0.8)	1 (0.2)	4 (6.7)		3 (0.8)	2 (0.9)	
GCS	15 (15–15)	15 (15–15)	15 (15–15)	<0.001*	15 (15–15)	15 (15–15)	0.003*
O2_saturation	94.31 ± 3.72	94.46 ± 3.51	92.95 ± 5.1	0.028+	94.93 ± 3.19	93.27 ± 4.3	<0.001+
MEWS	2 (1–3)	1.5 (1–2)	3 (2–3)	<0.001*	2 (1–2)	2 (1–3)	<0.001*
NEWS	4.43 ± 2.66	4.16 ± 2.56	6.83 ± 2.39	<0.001+	3.85 ± 2.44	5.4 ± 2.74	<0.001+
NEWS-2	4.45 ± 2.7	4.18 ± 2.58	6.8 ± 2.62	<0.001+	5 (3.25–7.75)	6 (4–8)	<0.001*
REMS	5.51 ± 2.5	5.26 ± 2.35	7.78 ± 2.69	<0.001+	5.11 ± 2.53	6.18 ± 2.31	<0.001+
qSOFA	1 (0–1)	1 (0–1)	1 (1–1)	<0.001*	1 (0–1)	1 (0–1)	<0.001*

Distribution percentages for sex, assisted ventilation and consciousness variables were given as column percentages. + Independent Samples t-test; * Mann–Whitney U Test Continuity Correction Yates Chi Square Test; ** Pearson Chi Square Test, ICU:Intensive care unit, SBP:Systolic blood pressure, DBS:Diastolic blood pressure, MAP:Mean arterial pressure, GCS:Glascow coma scale, MEWS: Modified early warning score, NEWS: National early warning score, NEWS 2: National early warning score 2, qSOFA: Quick sequential organ failure assessment

Table 2: Scoring Systems' Sensitivity and Specificity for Intensive Care Admission

	Sensitivity	Specificity	PPV	NPV	P
MEWS	0.66	0.791	0.26	0.95	<0.001
NEWS	0.917	0.587	0.19	0.98	<0.001
NEWS 2	0.883	0.583	0.19	0.97	<0.001
REMS	0.833	0.513	0.16	0.96	<0.001
qSOFA	0.800	0.615	0.19	0.96	<0.001

MEWS: Modified early warning score, NEWS: National early warning score, NEWS 2: National early warning score 2, qSOFA: Quick sequential organ failure assessment PPV: Positive predictive value, NPV: Negative predictive value

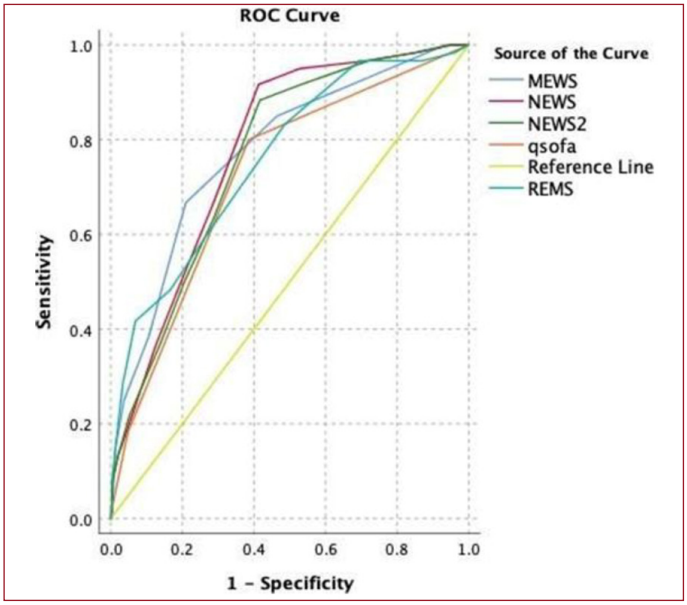

Figure 2. ROC Analysis of Scoring Systems for ICU Admission

ROC analysis was performed to evaluate the value of MEWS, NEWS, NEWS-2, REMS, and qSOFA scoring systems in predicting mortality in patients with COVID-19 (AUC:0.588, 0.658, 0.654, 0.638, and 0.577, respectively) (**Figure 3**). ROC analysis found a cut-off value of 1.5 for MEWS, 3.5 for NEWS, 3.5 for NEWS-2, 5.5 for REMS and 0.5 for qSOFA. The scoring systems' NPV at indicated specificity and sensitivity for predicting mortality were 0.61, 0.67, 0.67, 0.66, and 0.61 respectively, and were statistically significant (p<0.001) (**Table 3**). When patients were divided into two groups as those at high risk and low risk for mortality according to the specified cut-off values, the high risk categorization for each scoring system was associated with mortality (p<0.001) (**Table 2**).

Table 3: Scoring Systems' Sensitivity and Specificity for In-Hospital Mortality

	Sensitivity	Specificity	PPV	NPV	P
MEWS	0.566	0.547	0.50	0.61	<0.001
NEWS	0.689	0.526	0.53	0.67	<0.001
NEWS 2	0.685	0.523	0.53	0.67	<0.001
REMS	0.637	0.571	0.54	0.66	<0.001
qSOFA	0.502	0.634	0.52	0.61	<0.001

MEWS: Modified early warning score, NEWS: National early warning score, NEWS 2: National early warning score 2, qSOFA: Quick sequential organ failure assessment, PPV: Positive predictive value, NPV: Negative predictive value

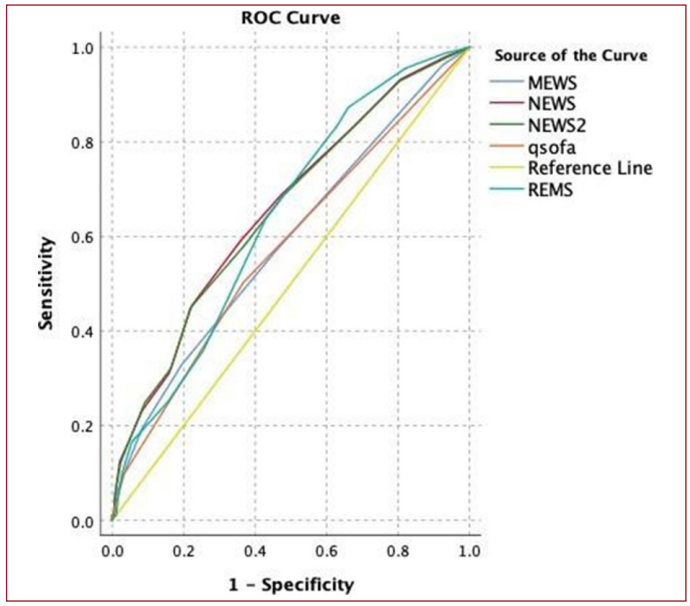

Figure 3. ROC Analysis of Scoring Systems for In-Hospital Mortality

DISCUSSION

Results of the present study demonstrated that MEWS, NEWS, NEWS 2, REMS and qSOFA early warning scoring systems were successful in predicting ICU admission and mortality for patients with COVID-19 who presented to the ED.

MEWS is a scoring system designed primarily for nurses to detect deterioration in patients. In addition, it can be used by any health professional with adequate training. This scoring system allows for the early detection of clinical deterioration and need for transition to ICU (14). One study by Covino et al. (15) found that MEWS was successful in excluding the need for ICU in patients with COVID-19 (Sensitivity:70, NPV:92.5), but was not associated with mortality. In the present study, we found that MEWS was similarly successful in excluding the need for ICU (sensitivity:0.66, specificity:0.79 and NPV:95); however, it was also significantly associated with mortality, despite low sensitivity and specificity (sensitivity:0.56, specificity:0.54).

NEWS has been originally developed to standardize assessments in the United Kingdom for early detection of clinical deterioration in patients. In this scoring system, patients with low scores can continue to receive usual care and monitoring, while patients with high scores should be considered for transition to ICU (16). One study by Smith et al. (16) that evaluated 35,585 patients in the United Kingdom and compared NEWS with 33 other EWS found NEWS to be superior to other scoring systems in predicting ICU admission and mortality in patients with COVID-19. The present study found that NEWS to be highly successful in both predicting and excluding the need for ICU admission (Sensitivity:0.917, NPV:0.98) and predicting and excluding mortality (Sensitivity:0.818, NPV:0.991). This result is in line with the literature.

In 2019, Smith et al. (17) added hypercapnic respiratory failure to NEWS parameters; the updated version, called NEWS-2, could can also be used for people with type 2 respiratory failure. However, hypercapnia is known to be rare in patients with COVID-19 including those admitted to the ICU (15, 18); furthermore, hypoxia caused by early pulmonary involvement is the most common clinical outcome in the course of the disease (19). Covino et al. (15) found that NEWS and NEWS-2 had similar effectiveness in predicting the need for ICU in COVID-19 patients, but NEWS was more successful than NEWS-2 in predicting mortality. Our study found that NEWS was more successful than NEWS-2 in predicting the need for ICU, while both had similar effectiveness in predicting mortality. The difference between these results can be explained by the length of follow-up: Covino et al based their assessments on ICU admission and mortality within 48 hours, while our study evaluated in-hospital ICU admission and mortality without any time restrictions.

REMS is used in pre-hospital settings to determine whether a patient can benefit from prompt access to advanced life support; and it is calculated with pre-hospital values or without laboratory tests (12). Covino et al. (15) found REMS to be a significant predictor of ICU admission and mortality, and showed that REMS had a high sensitivity (0.909) and NPV (0.99) for mortality. The present study also found REMS to be a significant predictor of ICU admission, with a sensitivity of 0.86, and a NPV of 0.96. However, for mortality, REMS was significant, but had low sensitivity and NPV (Sensitivity:0.637, NPV:0.66). This is thought to be caused by different length of follow-up in these two studies. Covino et al based their assessments on ICU admission and mortality within 48 hours, while our study evaluated in-hospital ICU admission and mortality without any time restrictions.

qSOFA scoring was designed as a simple and quick tool to predict mortality in patients with sepsis (20). Covino et al. (15) found that qSOFA was successful in predicting mortality in patients with COVID-19, but was clinically insignificant in predicting ICU admission (p=0.066). In the present study, qSOFA was found to be clinically significant in predicting both ICU admission and mortality, and was more successful in predicting ICU admission. qSOFA had a sensitivity of 0.80 and a NPV of 0.96 for ICU admission, and a sensitivity of 0.50 and a NPV of 0.61 for mortality. In the region where our hospital is located, there is a large number of elderly people and nursing homes. As a result, there is a high number of patients with dementia and neurological sequelae in our patient population. Therefore, altered mental status, one of the parameters in qSOFA, is seen frequently and this explains why qSOFA was significant in predicting the need for admission to ICU.

This study has some limitations as follows: EWS in the present study were calculated using patients' data from the first arrival at the ED, and the study ended with a single evaluation. However, repeated assessments at different time points could yield different results. Another limitation is the retrospective nature of the study. Prospective and multicenter studies are needed.

CONCLUSIONS

MEWS, NEWS, NEWS-2, REMS, and qSOFA, known as early warning scoring systems, were found to be clinically significant in identifying patients in need of ICU. High NPVs for each score indicates that these tools can be used for identifying patients who do not need ICU admission. MEWS, NEWS, NEWS-2, REMS, and qSOFA were clinically significant in predicting mortality. However, they were found to have low PPV and NPV, and this suggests that they cannot be used as stand-alone tools for predicting mortality, but can be helpful when used in conjunction with clinical evaluation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Katip Çelebi University Non-Intervential Clinical Trials Ethics Committee (Date: 27/05/2021, Decision No: 0265).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Comparison of Diagnostic Techniques Used in the Differential Diagnosis of Endometrial Pathologies Presenting with an Abnormal Uterine Bleeding

Anormal Rahim Kanaması ile Başvuran Endometrial Patolojilerin Ayırıcı Tanısında Farklı Tanı Tekniklerinin Karşılaştırılması

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Abstract

Aim: Transvaginal ultrasonography (TVUSG) examination, dilatation and curettage (D&C) approach and hysteroscopic assesment are frequently used in examination of the abnormal uterine bleeding (AUB). The specisific test for detection of the AUB is histopathological evaluation. The study aimed to check the exactness of TVUSG, D&C and hysteroscopy for differential diagnosis of the AUB.

Material and Method: Subjects with AUB, who were supposed to have an endometrial pathology on TVUSG, D&C or hysteroscopy, were included in this retrospective study. Our retrospective study was conducted in 160 patients who were admitted to our clinic with complaint of abnormal uterine bleeding. The final pathological diagnosis was accepted as the reference test and sensitivity and specifity of the D&C, hysteroscopy and TVUSG was checked with the pathological diagnosis.

Results: Hysteroscopy combined with biopsy provieded highest correlation with the histopathological evaluation. However, the statistical values obtained with TVUSG was comparable to that of the hysteroscopy alone and D&C but lower than that of the hysteroscopy combined with biopsy. This study examined 160 patients who applied to Medipol University Gynaecology and Obstetrics Clinic. The rate of those who have never conceived was 40.6%, 1 pregnancy was 16.3%, 2 pregnancies was 18.8%, nulliparity was most common, no history of abortus was in majority, 2 cases with 1 ectopic pregnancy and 3 cases with 2 ectopic pregnancy histories were detected. The mean double wall thickness of the endometrium was 10.9±3.7 mm. Hysteroscopic evaluation with a biopsy had highest specifity, sensitivity, positive and negative predictive values.

Conclusion: The goal of this study is to evaluate the worth of diagnostic techniques. An examination of the data from our investigation revealed the low sensitivity and specificity of transvaginal ultrasonography. Hysteroscopy is more accurate in diagnosing and treating submucous fibroids and endometrial polyps than TVUSG. H/S must adhere to TVUSG. The greatest diagnostic outcomes for the evaluation of endometrial diseases come from the combination of hysteroscopy and endometrial D&C. Multicenter research containing more patients is required to contribute more literately.

Keywords: Abnormal uterine bleeding, transvaginal ultrasound, dilatation and curretage, hysteroscopy

Öz

Amaç: Anormal uterin kanamanın (AUB) incelenmesinde transvajinal ultrasonografi (TVUSG) muayenesi, dilatasyon ve küretaj (D&C) yaklaşımı ve histeroskopik değerlendirme sıklıkla kullanılmaktadır. AUB tespiti için özel test histopatolojik değerlendirmedir. Çalışma, AUB'nin ayırıcı tanısı için TVUSG, D&C ve histeroskopinin doğruluğunu kontrol etmeyi amaçladı.

Gereç ve Yöntem: Bu retrospektif çalışmaya TVUSG, D&C veya histeroskopide endometrial patoloji olduğu düşünülen AUB'lu olgular dahil edildi. Retrospektif çalışmamız anormal uterin kanama şikayeti ile kliniğimize başvuran 160 hasta üzerinde yapıldı. Son patolojik tanı referans test olarak kabul edildi ve patolojik tanı ile D&C, histereskopi ve TVUSG'nin duyarlılık ve özgüllüğü kontrol edildi.

Bulgular: Biyopsi ile birlikte histeroskopi, histopatolojik değerlendirme ile en yüksek korelasyonu sağladı. Bununla birlikte, TVUSG ile elde edilen istatistiksel değerler, tek başına histeroskopi ve D&C ile karşılaştırılabilir, ancak biyopsi ile kombine histeroskopiden daha düşüktü. Bu çalışmada Medipol Üniversitesi Kadın Hastalıkları ve Doğum Kliniği'ne başvuran 160 hasta incelenmiştir. Hiç gebe kalmayanların oranı %40,6, 1 gebelik %16,3, 2 gebelik %18,8, en sık nulliparite, hiç abortus öyküsü çoğunlukta, 2 olgu 1 ektopik gebelik ve 3 olgu 2 ektopik gebelik öyküleri tespit edildi. Endometriyumun ortalama çift duvar kalınlığı 10.9±3.7 mm idi. Biyopsi ile histeroskopik değerlendirme en yüksek özgüllük, duyarlılık, pozitif ve negatif prediktif değerlere sahipti.

Sonuç: Transvajinal ultrason, AUB'ye yol açan endometrial patolojilerin değerlendirilmesinde kolayca bulunabilen ve tekrarlanabilir bir görüntüleme tekniğidir. Ancak TVUSG'nin özgüllüğü oldukça düşüktür. Çalışma popülasyonumuzdaki endometriyal patolojileri doğru bir şekilde saptamak için kullanılan yöntemler arasında en yüksek duyarlılık ve özgüllük biyopsi ile birlikte histerosopi ile elde edilmiştir. Yine de TVUSG, tek başına histeroskopi ve D&C ile karşılaştırıldığında benzer istatistiksel değerler sağlar. Çalışmamızda amacımız tanısal yöntemlerin değerini belirlemektir. Literatüre katkısı açısından çok merkezli ve daha çok sayıda hastanın yer aldığı araştırmaların yapılması gerekmektedir.

Anahtar Kelimeler: Anormal uterin kanama, transvajinal ultrason, dilatasyon ve küretaj, histeroskopi

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INTRODUCTION

Changes in the endometrial layer lining the uterine cavity occur due to hormonal and non-hormonal etiologies.[1] Some of these might be in neoplastic or non-neoplastic origin.[2] These pathologies appear clinically as abnormal uterine bleeding (AUB). Considering the applications to gyneacology outpatient clinics, AUB is a significant problem.

Abnormal uterine bleeding is the general definition of deviations from the normal menstrual cycle pattern and is an important clinical condition that can emerge for different reasons.[3] A normal menstrual cycle lasts between 28 +/- 7 days (21-45 days for adolescents), of which bleeding occurs in approximately 2-6 days.[4] The amount of bleeding is on average 20-60 mL/cycle. There might be differences in the menstrual cycle duration in the reproductive period. Abnormal uterine bleedings seen during and after the reproductive period are clinically grouped under 8 headings; oligomenorrhea, polymenorrhea, hypermenorrhea (menorrhagia), hypomenorrhea, metrorrhagia, menometrorrhagia, contact bleeding (Postcoital bleeding, postmenopausal bleeding. The prevalence of anovulatory cycles increases under the age of 20 and above the age of 40. 50% of the applicants with AUB are in the peri-postmenopausal period, 30% are in the reproductive period, and remaining 20% are in the adolescence period.[2]

FIGO (International Federation of Gynecology and Obstetrics) defined AUB terminology according to the distribution of symptoms in 2011 as heavy menstrual bleeding (HMB), intermenstrual (IMB) bleeding and their combinations.[5] The causes of AUB were grouped under two groups as uterine structural anomalies and non-structural anomalies. The first group includes pathologies such as polyps, adenomyosis, leiomyoma, hyperplasia and, malignancy while the second group includes coagulopathies, ovarian dysfunction, endometrial, iatrogenic and unclassified anomalies (PALM-COEIN, 3).

The priority in diagnosis is to identify the underlying pathology in order to exclude pregnancy and cancer and to provide appropriate treatment.[4] The anamnesis should be detailed and include important questions to explain the etiology of bleeding.[5] Age, pregnancy history, contraception status, last menstruation date, menstrual interval, duration and bleeding pattern, non-menstrual bleeding, other bleeding-related signs (anemia) and symptoms, postcoital bleeding/pain, type of discharge if present, history of trauma, drug intake, chronic stress, body weight changes, systemic diseases are essential for preliminary diagnosis.[5] After primary anamnesis and physical examination are performed an interventional/ noninterventional diagnostic technique is usually required. Transvaginal ultrasonography (TVUSG) is preferred as an easy-to-use, non-invasive imaging method for diagnosis of AUB.[6] Transvaginal ultrasonography is also useful in detecting uterine and adnexial pathologies.[6] It is a diagnostic tool that guides the invasive procedures that might be required for a definitive diagnosis. Dilatation and curettage (D&C) is also used to reach the diagnosis by performing endometrial sampling and could be executed in outpatient clinic conditions.[7] Hysteroscopy (H/S), on the other hand, is a minimally invasive diagnosis and treatment method that directly evaluates endometrial pathologies and allows visual sampling and/or intervention.[8] All these techniques could be used alone or in combination to reach a diagnosis. Yet histopathological evaluation is golden standard for final diagnosis. So knowledge of predictive value of each diagnostic method gains importance in choice of diagnostic tool for clinical practitioner. Depending on these; we aimed to evaluate the endometrial pathologies in a group of Turkish patient population with AUB using TVUSG, D&C, and H/S methods, and to compare the predictive value of each technique by comparing their estimation of accurate diagnosis reached by gold standard histopathological evaluation.

MATERIAL AND METHOD

Among the patients who applied to Medipol University Faculty of Medicine, Department of Obstetrics and Gynecology with the complaint of AUB, 160 patients who met criteria were included. A total of 160 patients (aged; 38±7, 21-68 years) included in the study were evaluated with TVUSG, D&C and operative H/S. Ethical approval for study was obtained from the Ethics Committee of Medipol University Non-Invasive Clinical Researches. The study was performed in retrospective manner. Diagnostic methods used during examination and diagnosis were compared with those who were diagnosed with histopathology (with normal results (29 people), endometrial polyp (81 people), endometrial hyperplasia (27 people), leiomyoma (21 people), endometrial cancer (2 people)).

Demographic, radiological and histopathological findings of the patients were obtained from the archive records. The age, gravida and parity history of the patients, the mode of delivery if they gave birth, abortion and ectopic pregnancies were recorded as study data. TVUSG, D&C, and/or H/S evaluation was required as criteria for inclusion. Whether the patients had intrauterine devices, oral contraceptive use, previous gynaecological surgeries and intervention information were noted. Systemic physical examination and gynaecological examination findings of each patient were also recorded.

Transvaginal ultrasoonographic evaluation was performed using General Electric Logiq brand ultrasound and 8-11 mHz vaginal probe. Double wall endometrial thickness was measured while the uterus was viewed in the sagittal plane. When uterine sagittal and coronal planes were evaluated, hyperechogenic focal thickenings were defined as endometrial polyps, and lesions with more heterogeneous hypoechogenicity (close to myometrial echogenicity) in the cavity compared to polyps were defined as submucous leiomyoma.

As a H/S instrument, an operative 5 mm rigid hysteroscope from Karl Storz company (Germany) was used. Hysteroscopy was performed under general anesthesia in operating room conditions. After the cervix and vagina

were cleaned with povidone iodine solution while the patients were in the dorsolitotomy position, the uterine cavity was entered with a resectoscope by holding it at 11 o'clock with a single gear and dilating it up to the 9-10 hegar bougie. Cavity distention was achieved with mannitol (resectisol) or 0.9% NaCl (physiological saline) solutions. The appearance of the endometrium, whether it was compatible with the menstrual phase, the presence of pathologies occupying uterine cavity, uterine anomalies and both ostia were recorded. Endometrial polyp was defined as a smooth-surfaced, pedunculated or broad-based soft structure, and submucous leiomyoma was defined as shiny, psoriatic, usually broad-based, hard and vascularized lesions covered by the endometrium. If the endocervical canal, endometrial cavity, and right and left tubal ostia could be evaluated, the procedure was considered adequate and these cases were included in our study. Tissue sampling was done from suspicious areas. These materials were sent to pathology in 10% formaldehyde solution and were evaluated histopathologically. Patients with adhesions in the cavity, intramural myomas displacing the cavity and congenital anomalies were not included in our study. Definitive diagnosis was made according to histopathological results.

Sensitivity, specificity, positive and negative predictive values were calculated separately for TVUSG, H/S biopsy and D&C procedures.

Version 21.0 of the SPSS (Statistical Package or the Social Sciences) program (IBM, Armonk, NY, USA) was used for statistical analysis of the data. Descriptive statistics were expressed as mean±standard deviation or median (minimum-maximum) for discrete and continuous numerical variables, and number of cases and (%) for categorical variables. Cross-table statistics were used to compare categorical variables (Chi-square). A p value <0.05 was accepted as threshold for statistical significance.

RESULTS

This study was carried out on 160 cases who applied to Medipol University Gynaecology and Obstetrics Clinic. Obstetric and pregnancy history of patients are presented in **Table 1**. The rate of those who have never conceived (nulligravid) was 40.6% (n:65), 1 pregnancy was 16.3% (n:26), 2 pregnancies was 18.8% (n:30). In means of parity; nulliparity was most common (54.4%, n:87), followed by 2 and 1 parities (18.8%, 11.3%, n: 30, 18 respectively). Patients with no history of abortus were in majority (76.9%, n:123) followed by 1 and 2 abortions (15%, 3.1%, n:24, 5 respectively). While there was no ectopic pregnancy history in 96.9% (n:155) of our patients, 2 cases with 1 ectopic pregnancy and 3 cases with 2 ectopic pregnancy histories were detected. None of the patients with birth history had both normal vaginal delivery and C-section history, while normal vaginal delivery was more common compared to C-section (n: 54 vs 21 respectively).

Table 1. Demographic features of the study subjects

Age, years	38±7
Menopause, n	0.0812
Gravida, n	1.51 ± 0.35
Parity, n	1.09 ± 0.4
Abortus, n	0.43 ± 0.28
Ectopic pregnancy, n	0.051 ± 0.023
Vaginal delivery rate	0.85 ± 0.019
C-section rate	0.243 ± 0.123
Endometrial thickness, mm	10.9 ±3.7

Data are presented as mean ± standard deviation

Transvaginal ultrasonography preliminary diagnosis findings of patients were as follows; normal (34.4%, n:55), endometrial polyp (36.3%, n:55), endometrial hyperplasia (23.1%, n:37), leimyomotosis (6.3%, n:10). The mean double wall thickness of the endometrium was found to be 10.9±3.7 mm. Hysteroscopic preliminary diagnosis findings of patients were as follows; normal (28.2%, n:46), endometrial polyp (43.1%, n:69), endometrial hyperplasia (19.4%, n:31), leimyomotosis (8.8%, n:14). Dilatation and curettage preliminary diagnosis findings of patients were as follows; normal (35.6%, n:57), endometrial polyp (38.3%, n:61), endometrial hyperplasia (19.7%, n:30), leimyomotosis (6%, n:10), endometrial cancer (1.2%, n:10). We also analyzed patients' H/S biopsy results and observed that preliminary diagnosis were as follows; normal (23.1%, n:37), endometrial polyp (50.6%, n:81), endometrial hyperplasia (13.1%, n:21), leimyomotosis (13.1%, n:21, **Table 2**). Final histopathological findings were as follows; normal (23.1%, n:37), endometrial polyp (50.6%, n:81), endometrial hyperplasia (21%, n:13.1), leimyomotosis (14.3%, n:23) and endometrial cander (1.2%, n:2). Crossectional comparison of each method with histopathological findings are presented in **Table 3**. Specifity, sensitivity, positive and negative predictive values for each diagnostic tool are presented in **Table 4**. Hysteroscopic evaluation with a biopsy had highest specifity, sensitivity, positive and negative predictive values (**Table 4**).

Table 2. Initial diagnosis obtained with several diagnostic methods and the definitive diagnosis provided by histopathological assessment

	Transvaginal Ultrasonography	Hysteroscopy	Hysteroscopy with biopsy	Dilatation and Curettage	Definitive diagnosis with histopathology
Normal	55 (34,4%)	46 (28,8%)	37 (23,1%)	57 (35,6%)	29 (18,1%)
Endometrial polyp	58 (36,3%)	69 (43,1%)	81 (50,6%)	61 (38,3%)	81 (51%)
Endometrial hyperplasia	37(23,1%)	31(19,4%)	21 (13,1%)	30 (18,7%)	27 (16,7%)
Leiomyoma	10 (6,3%)	14(8,8%)	21 (13,1%)	10 (6,0%)	21 (13.1%)
Endometrial Cancer	0,00	0,00	0,00	2 (1.2%)	2 (1.2%)

Table 3: Comparison of TVUSG, H/S and D&C preliminary and histopathological definitive diagnosis

	Histopathological diagnosis				
	Normal	E. polyp	E. hyperplasia	Leiomyom	Cancer
TVUSG					
Normal	24	10	16	5	
E. polyp	1	51	3	3	2
E. hyperplasia	4	15	7	9	
Leimyomotosis	-	5	1	4	
H/S					
Normal	27	1	16	1	
E. polyp	-	66	1	2	2+
E. hyperplasia	2	14	10	4	
Leimyomotosis	-	-	-	2	
H/S pathology					
Normal	29	-	6	-	
E. polyp	-	81	-	-	
E. hyperplasia	-	-	21	-	
Leimyomotosis	-	-	-	21	2
E. Cancer	-	-	-	-	
D&C					
Normal	24	22	-	11	-
E. polyp	2	59	-	-	-
E. hyperplasia	-	-	30	-	-
Leimyomotosis	1	-	-	9	-
E. cancer	-	-	-	-	2

Table 4. Diagnostic accuracy of the different diagnostic techniques (Histopathological results have been accepted as the definitive diagnosis)

	Sensitivity	Specificity	PPV	NPV
TVUSG	82.7%	83.9%	53.3%	95.6%
Hysteroscopy	93.1%	86.2%	60.0%	98.2%
Hysteroscopy with biopsy	100.0%	87.2%	78.0%	100.0%
D&C	88.8%	75.1%	42.1%	97.8%

TVUSG= Transvaginal ultrasonography, D&C= Dilatation and curettage, NPV= Negative predictive value, PPV= Positive predictive value

DISCUSSION

It is known that one third of the patients who apply to gynaecology outpatient clinics present with the complaint of AUB.[6] Endometrial pathologies are most commonly encountered as AUB in clinical practice. Abnormal uterine bleeding is the second most common complaint of gynaecologists after vaginal infections. When the perimenopausal/ postmenopausal age groups are considered together, AUB constitutes 69% of the complaints requiring gynaecological referral.[7] The biggest challenge in patients with AUB is to differentiate between those with dysfunctional uterine bleeding who only need medical treatment, and those with organic lesions that will require surgery. Different incidences of anatomical causes of AUB are seen in the literature.

In the literature, benign anatomical pathologies such as polyps, submucous fibroids and endometrial hyperplasia were found in 30-50% of cases in women with AUB, malignant pathologies were found in around 1% of patients under 50 years of age and 10-15% of patients over 50 years of age.[8] In our study, no correlation of age on endometrial pathologies was observed.

Diagnostic tests often do not provide a 100% definitive diagnosis, but they provide enough information to rule out a diagnosis possibility and help to identify the tests that are likely to make a definitive diagnosis. Transvaginal ultrasonography is an easy diagnostic technique used in the detection of endometrial pathologies and can be easily applied in outpatient settings. It provides recognition of uterine pathology in the majority of cases in women with postmenopausal bleeding and menstrual irregularities. Therefore, it is used for first-line examination.[9] However, the specificity of endometrial thickness measurement with TVUSG in premenopausal women is low and it is not suitable for detecting intracavitary abnormalities.[10] In our study, the sensitivity of TVUSG was calculated as 82.7% and the specificity as 83.9%, which is similar with the current literature.[10] Transvaginal ultrasonography, which is a non-invasive diagnostic tool in the diagnosis of AUB, can be preferred to techniques such as D&C in detecting endometrial abnormalities. However, TVUSG fails to differentiate endometrial abnormalities such as endometrial polyps, fibroids, and blood clots, and its diagnostic sensitivity is low, varying between 88% and 96%.[11] In our study, the preliminary diagnosis of polyps by TVUSG was found in 87.9% and is compatible with the literature.

Karlsson et al. has reported that the double-wall endometrial thickness measurement of 20 mm and above, that was performed in 759 endometrial cancer patients, was found to be associated with cancer.[12] In our study the mean double wall thickness of the endometrium was found to be 10.9±3.7 mm and measurement of 2 cancer cases were less than 20 mm (mean 10 mm). Alborzi et al. reported the sensitivity, specifity, positive and negative predictive values for TVUSG as followed; 72%, 92%, 94%, 65% respectively. In a metaanalysis that included 19 prospective studies, it was reported that the accuracy of TVUSG in detecting endometrial lesions was compared with the histopathological results obtained after hysteroscopy and hysterectomy, with a sensitivity between 46% and 100% and a specificity between 12% and 100%.[13] In our study, the sensitivity, specificity, PPD and NPV calculated for the preliminary diagnosis of TVUSG were found to be 82.7%, 83.9%, 53.3% and 95.6%, respectively. It seems to be compatible with the previous studies. The variability in these obtained values may be due to the TVUSG experience of the practitioners, their interpretation of the observed lesions, the number and diversity of cases, and the difference in reference tests. In addition, the patient's menstruation or menopausal status is one of the most important reasons for this difference. The fact that the endometrial thickness varies as a result of hormonal effects that differ according to the phases of the cycle in menstruating patients might cause small lesions not to be visualized in the thickening endometrium or a thick endometrium might feel like a lesion on its own and cause misinterpretations. This may be the most important reason for the difference in sensitivity and specificity of TVUSG reported in the literature.[14] In a study previous carried by Emanuel et al. stated that TVUSG and H/S combined and supported with histological evaluation, is the most appropriate reference technique for the evaluation of endometrial pathologies.[15]

Benign anatomical pathologies such as polyps, submucous fibroids and endometrial hyperplasia were found in 30-50% of cases in women with AUB while malignant pathologies were found in 1% of patients under 50 years of age and 10-15% of patients over 50 years of age.[16] In our study, no evaluation was made according to age difference. The limited number of cases and the low number of malignancies may be considered as a limiting factor.

Hysteroscopy enables gynaecologist to visualize the endometrial cavity for any endometrial or endocervical pathology. In modern obstetrics and gynaecology, instead of blindly performing D&C or endometrial biopsy, targeted biopsy with H/S, to investigate possible intrauterine disease, or the endometrial cavity, is a commonly preferred method. Hysteroscopy is considered as a "gold standard" technique for the evaluation of the uterine cavity and the detection of intrauterine pathologies.[17]

Lo et al. reported that H/S results without biopsy for endometrial carcinoma and hyperplasia have low sensitivity for diagnostic value. The authors stated that the combination of H/S with biopsy would increase the accuracy of the results.[18] The combined use of H/S and endometrial biopsy can give 100% accurate results in early diagnosis.[19] In our study, it was seen that it has 100% diagnostic value in those who underwent hysteroscopic biopsy. Gimpleson and Rappold suggested that H/S may be superior to D&C in the diagnosis of pathological conditions within the uterine cavity.[20] In the results obtained in our study, it was revealed that visual material removal with hysteroscopy is superior to dilatation and curettage, where the lesion is removed without being seen. The specificity and positive predictive value of hysteroscopy in cases with AUB has been found close to 100% in some studies. Compared to D&C alone, especially endometrial polyps and submucous fibroids can be recognized with greater precision.[21] We made the same evaluation with the results obtained from our study. Many studies have reported that H/S is more valuable than D&C in the diagnosis of AUB.[22] Although submucous fibroids and polyps, especially those close to the fundus and cornu, cannot be diagnosed during curettage, they are easy to diagnose with H/S. Classical D&C fails to detect 25% of lesions on the endometrial surface.[23] According to the data of our study, this rate has emerged as 25% difference for polyps and close to 100% for fibroids. Gimpelson et al. reported that H/S and direct biopsy for endometrial pathologies were more successful than D&C procedures.[24] In our study, hysteroscopic diagnosis rates of polyps and fibroids were 50.6% and 13.1%, respectively, while these rates were 38.3% and 6% with dilatation and curettage.

Endometrial polyps were detected in 81 of 160 patients included in our study. 22 of these cases could not be detected by D&C so we can propose that D&C alone may not be an ideal diagnostic tool for the diagnosis of AUB. The sample taken may be insufficient, and 10 to 35% of endometrial lesions may not be accurately diagnosed.[25] In our study, this rate was found to be 27%. Madan et al reported that H/S was more sensitive than D&C in recognizing endometrial polyps and submucous fibroids, but less sensitive in recognizing endometrial hyperplasia and endometrial carcinomas.[26] In our study we also observed findings consistent with this study. The sensitivity, specificity, PPD and NPD values of H/S pathology results were found to be 100%, 87.2%, 78% and 100%, respectively, D&C values were inferior to these resılts. We observed that H/S was superior to D&C for diagnosis of polyps and submucous myomas.

In our study, the sensitivity of TVUSG in diagnosing endometrial polyps was 87.9% and specificity 83.9%. On the other hand, we observed that the sensitivity and specifity of H/S alone were 93.1% and 86.2% respectively while H/S combined with tissue sampling had 100% and 87.2% for same parameters respectively (**Table 4**). Salim et al. evaluated the performance of TVUSG, sonohysterography (SHG), and H/S for diagnosis of endometrial polyps in a group of 5000 patients. They reported the sensitivity of each tool as; 91%, 95%, 90% and the specificity of each tool as; 90%, 92%, and 93%, respectively. The advantage of SHG over H/S is that it can show adnexial masses and intramural components of leiomyomas.[27] Kilinc et al. compared TVUSG and H/S for the evaluation of endometrial pathologies in a group of 116 patients. They reported sensitivity and specifity for each method as 78.26%-51.35% and 85.51% - 67.57%, respectively.[28]

Endometrial hyperplasia is the proliferation of endometrial glands in irregular shape and size. It is an atypical cellular increase in the ratio of gland-stroma compared to the normal proliferative endometrium. It occurs as a result of dysregulation in estrogen/progesterone balance.[29] In a study evaluating the risk of endometrial cancer in women with endometrial hyperplasia with and without atypia, authors reported increased risk in patients with cellular atypia (28% vs 5%.[30] Most women with endometrial hyperplasia with atypia might also have endometrial cancer at the same time.[31] In a study of 2572 patients, endometrial cancer with atypia was also found in the hysterectomy results of 37% of the patients whose endometrial biopsies had a result of endometrial hyperplasia with atypia alone.[32] Therefore, the diagnosis of endometrial hyperplasia, which is a premalignant lesion, is very important for clinical practice. In our study, endometrial hyperplasia was reported with a rate of 16.7% in 27 cases according to the histopathological definitive diagnosis. Endometrial hyperplasia was detected in 16 of 55 cases who were preliminary diagnosed with normal endometrium in TVUSG. Endometrial hyperplasia was detected in 16.2% of 37 cases whose biopsy results were reported as normal H/S.

In the literature, the incidence of submucous myoma has been reported to be 6-10%.[33] Uterine leiomyomas (fibroids) are the most common pelvic tumor in women. Submucous leiomyomas are an important cause of AUB and might cause anemia.[34] In our study, 13% submucous myoma was detected

in 21 cases according to the histopathological definitive diagnosis. Submucous leiomyoma detected as a result of a combination of H/S and biopsy was found in 11 (19.3%) of the biopsy results reported as normal by D&C. Hysteroscopy seems superior to D&C in detecting intracavitary uterine lesions. D&C is also considered superior to H/S-guided biopsy in the detection of cancer and diagnosis of endometrial hyperplasia

CONCLUSION

This study's objective is to assess the value of diagnostic methods. Transvaginal ultrasonography has low sensitivity and specificity, according to an analysis of the data from our study. In cases of submucous fibroids and endometrial polyps, hysteroscopy performs diagnostic and therapeutic tasks more accurately than TVUSG. H/S ought to follow TVUSG. The combination of hysteroscopy and endometrial D&C yields the best diagnostic results for the assessment of endometrial pathologies. To make a greater literary contribution, multicenter studies involving more patients are necessary.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medipol University Ethics Committee (Date: 10/08/2017, Decision No: 10840098-604.01.01-E26932).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article / Orijinal Araştırma

Global Scientific Outputs of Psychiatric Malpractice Publications: A Bibliometric Approach From 1980 To 2022

Psikiyatrik Malpraktis Yayınlarının Küresel Bilimsel Çıktıları: 1980'den 2022'ye Bibliyometrik Bir Yaklaşım

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Abstract

Aim: Until recent years, psychiatry was a medical field that faced malpractice relatively less than other fields. However, the increase in malpractice cases worldwide and the fact that psychiatrists are on the agenda has created a need for more knowledge and experience. The aim of the study is to evaluate the scientific outputs of psychiatric malpractice as a holistic perspective.

Material and Method: Publications on psychiatric malpractice between 1980 and 2022 were analyzed. The data of the publications were accessed from the Web of Science database, and in the first stage of the research, the quantitative data in this area were examined with performance analyzes. In the second stage, visual network maps that reveal the links of the publications were created using the VOSviewer package program.

Results: A total of 426 publications, 312 of which were articles, and 8901 citations on psychiatric malpractice were reached during the specified dates. The most productive country in this field was the United States with 279 publications, and the most productive institution was Harvard University with 46 publications. The most active research area on this subject was psychiatry with 219 publications, and the journal with the highest number of publications was The Journal of the American Academy of Psychiatry and the Law with 35 publications. The most productive authors were Scott C with 11 publications and Gutheil TG with 10 publications.

Conclusion: This comprehensive bibliometric analysis study focused on publications on psychiatric malpractice and, to our knowledge, is the first bibliometric analysis in this field. We believe this study will provide a holistic perspective to the publications of psychiatric malpractice and guide the researchers interested in this field.

Keywords: Malpractice, psychiatry, forensic psychiatry, bibliometric analysis, ethics

Öz

Amaç: Psikiyatri, tıbbın diğer alanlarına göre malpraktis sorunlarıyla son yıllara kadar görece daha az yüzleşen bir tıbbi branş olarak bilinmekteydi. Fakat malpraktis davalarının tüm dünyada artış göstermesi ve günümüzde bu konunun psikiyatristler için de sıklıkla gündeme gelmesi daha fazla bilgi ve deneyim ihtiyacını doğurmuştur. Bu araştırmadaki amaç psikiyatrik malpraktis konusundaki literatür verilerini bütüncül bir bakış açısıyla ve bibliyometrik yöntemlerle değerlendirmektir.

Gereç ve Yöntem: 1980-2022 yılları arasında psikiyatrik malpraktis konusunda yapılmış yayınlar analiz edilmiştir. Yayınlara ait verilere Web of Science veri tabanından ulaşılmış olup araştırmanın ilk aşamasında performans analizleriyle bu alandaki sayısal veriler incelenmiştir. İkinci aşamada ise VOSviewer paket programı kullanılarak yayınlara ait bağlantıları ortaya koyan görsel ağ haritaları oluşturulmuştur.

Bulgular: Belirlenen tarihler aralığında psikiyatrik malpraktis konusunda 312'si makale olmak üzere toplam 426 yayın ve 8901 atıfa ulaşılmıştır. Bu alanda en üretken ülke 279 yayın ile ABD, en üretken kurum ise 46 yayın ile Harvard Üniversitesi'ydi. Bu konuda en aktif araştırma alanı 219 yayınla psikiyatri olup, en çok yayına sahip dergi ise 35 yayın ile The Journal of the American Academy of Psychiatry and the Law'dı. Bu alanda en üretken yazarlar 11 yayınla Scott C ve 10 yayınla Gutheil TG'dı.

Sonuç: Bu kapsamlı bibliyometrik analiz çalışması psikiyatrik malpraktislere yönelik yayınlara odaklanmış olup, bildiğimiz kadarıyla bu alanda yapılan ilk bibliyometrik analizdir. Bu çalışmanın psikiyatrik malpraktis alanındaki yayınlara bütüncül bir bakış açısı sağlayarak bu alanla ilgilenen araştırmacılara yol gösterici olacağına inanmaktayız.

Anahtar Kelimeler: Malpraktis, psikiyatri, adli psikiyatri, bibliyometrik analiz, etik

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INTRODUCTION

Medical conditions that occur as a result of failure to provide standard treatment and care due to negligence, lack of knowledge and skills, or inattention to the patient are called malpractice.[1] Medical errors can occur in any area where the patient and health service are present, and the patient-physician relationship and legal regulations in this area are becoming more and more important. There are many reasons for the emergence of malpractice, such as the absence of the necessary quality and number of healthcare personnel, increased patient load, negative working conditions, lack of cooperation in consultations, neglect of ethical rules and administrative problems, depending on the healthcare workers or healthcare system.[2,3] While psychiatry is accepted as a medical specialty with a relatively low risk in terms of medical malpractice, it is known that there has been a rapid increase in malpractice lawsuits filed against psychiatrists in recent years due to medical negligence reports, malpractice and ethical violation claims.[3-5] In a study conducted in the United States, examining 17 medical specialties, it was determined that 7.5% of physicians are exposed to malpractice lawsuits each year, and approximately 3% of these are related to the field of psychiatry.[6] Due to the fear of exposure to malpractice lawsuits, physicians act overprotective or hesitant, use diagnostic and therapeutic medical practices unnecessarily, and avoid practices with a high risk of resulting in malpractice lawsuits. This situation, which is called defensive medical practices, has become very popular among physicians in recent years, secondary to the increasing malpractice cases. It is thought that a simultaneous change in the perspectives and behaviors of health professionals and patients is necessary to reduce defensive medical practices. In addition, the development of clinical practice guidelines specially prepared for risky clinical situations and their use in routine clinical practices can reduce both malpractice and defensive medical practices.[7]

In areas where physicians lack sufficient data, bibliometric approaches become more important in terms of quantitative evaluation, research impact, and guiding contemporary literature investigations.[8] Bibliometric analysis is a research method in which the publications produced by authors or institutions in a spesific field and time period and the connections between these publications are revealed.[9] Despite the increasing malpractice cases, it is seen that there is not enough research in the literature both in the field of general medical malpractice and in the field of psychiatric malpractice.[10] Although there have been bibliometric studies on general malpractice, it appears that no such study has been performed yet on psychiatric malpractice.[11] This situation makes it difficult for health professionals in the field of psychiatry to reach sufficient knowledge and experience on the subject. In this context, our study aims to guide clinicians and researchers who are interested in this field by providing a holistic perspective to the studies in the field of psychiatric malpractice.

MATERIAL AND METHODS

On 11.01.2023, the words "psychiatry AND malpractice OR psychiatric malpractice OR malpractice in psychiatry" were searched in the Web Of Science Core Collection database without using any exclusion criteria in all fields, and the publications in this field were accessed. No filtering was used in the search, all times (1980-2022) and all publications were included. In the first stage, the quantitative data of the publications in this field were examined with the performance analyses made on the Web of Science.

In the second stage of the study, visual network maps of the publications in the related field were obtained by using the VOSviewer package program (Version 1.6.17, Leiden University's Center for Science and Technology Studies). VOSviewer package program is one of the analysis programs that stand out with its user-friendly interface in terms of visual mapping of bibliometric data. Correlation analyses between the number of articles produced by the countries and their economic and development indicators of GDP (Gross Domestic Product), GDP PPP (Purchasing Power Parity) (data was obtained from the World Bank Group website - 2021 data),[12] and HDI (Human Development Index) (data was obtained from the United Nations Development Programme Human Development Report 2021-2022)[13] were analyzed using the Spearman correlation coefficient. Additionally, the "https://app.datawrapper.de" website was used for the world map image.

Ethics committee approval was not obtained since it was not a human or animal study and was conducted on publicly available publications.

RESULTS

As a result of the search in the Web Of Science Core Collection database, a total of 426 publications covering the years 1980-2022 were reached. The three research area with the greatest number of products on psychiatric malpractice were psychiatry (n=219, 51.4%), government law (n=73, 17.1%), and psychology (n=53, 12.4%).The authors with the largest number of publications in the field were Scott C. (n=11, 2.5%) and Gutheil TG. (n=10, 2.3%), with 11 and 10, respectively. The most frequent type of publications in this field were articles with 312 (73.2%) records and reviews with 39 (9.1%) records.

The United States was the most productive country in this field with 279 (65.4%) publications. The United States is followed by England (4.4%) and Germany (4.4%) with 19 publications each. In **Figure 1**, there was a world map colored reflecting the number of publications of the countries. There was a statistically significant correlation between the number of publications produced by the countries about psychiatric malpractice and their GDP, GDP PPP, and HDI indicators ($r=0.670$, $p<0.001$; $r=0.521$, $p=0.004$, $r=0.489$, $p=0.003$ respectively).

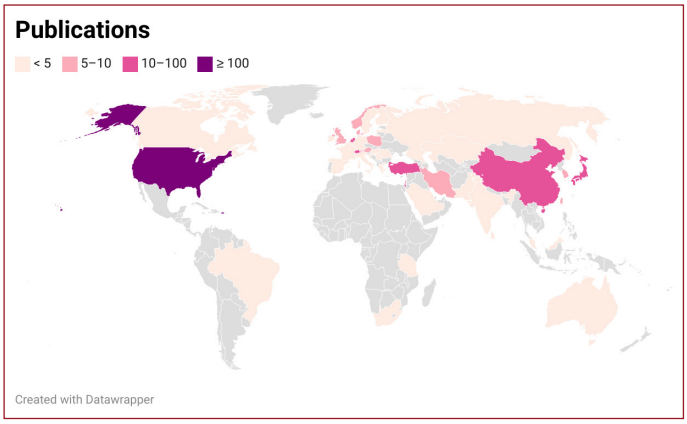

Figure-1: The world map of publications

The institutions with the highest number of publications on psychiatric malpractice are Harvard University (n=46, 10.7%) and Harvard Medical School (n=33, 7.7%) (**Table 1**).

Table 1. The most productive institutions by the number of publications

Affiliations	Record Count	% of 426
Harvard University	46	10.7
Harvard Medical School	33	7.7
The University of California System	27	6.3
Us Department of Veterans Affairs	24	5.6
Veterans Health Administration Vha	24	5.6
The University of Texas System	16	3.7
Yale University	15	3.3
The University of California Los Angeles	14	3.2
The University of Illinois Chicago	13	3.0
The University of Illinois System	13	3.0

*Showing 10 out of 69 institutions.

The journals with the highest number of publications in this field were The Journal of the American Academy of Psychiatry and the Law (n=36, 8.2%) and The American Journal of Psychiatry (n=19, 4.4%).

There were 8,901 citations to a total of 426 publications, including 8,596 (96.5%) non-self citations. When the publications and citations were sorted by year, it was seen that the year with the highest number of publications and citations was 2021 with 21 (4.9%) publications and 1158 (13.0%) citations. With 18 (4.2%) publications each, 2009 and 2011 were the other productive years and these years had 180 (2.01%) and 220 (2.4%) citations, respectively (**Figure 2**).

The most cited authors were Adler NE, Moore PJ, and Robertson PA with 115 citations each. Authors with at least 1 publication were included in the citation network layer analysis. It was determined that there were 14 linked authors and a citation network layer map was created. The colors of the circles indicate the authors' publications' timeliness, while the lines reflect the connections between the authors (**Figure 3**). In the resulting network map, the authors were divided into 5 clusters and the authors with the highest total link strength were Meyer DJ, Reich J, Shatzberg A and Slawson PF.

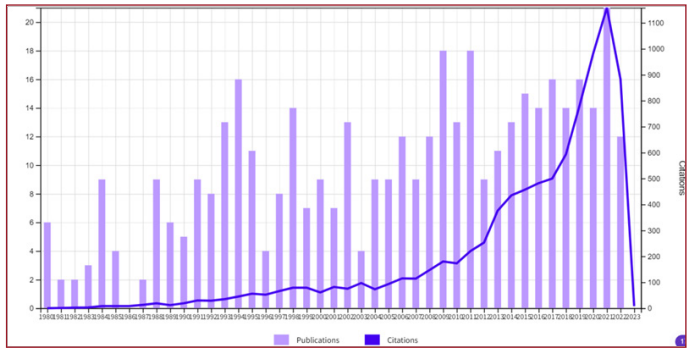

Figure-2: Number of publications and citations by year

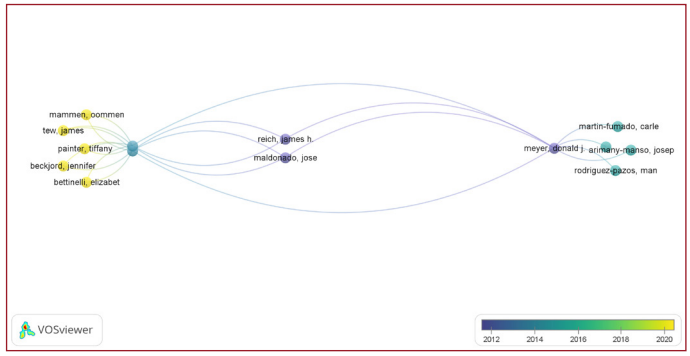

Figure-3: Citation analysis network layer map in the context of authors

The most frequently used keywords according to the keyword network map created by including 78 keywords used at least once were; "malpractice", "psychiatry" and "forensic psychiatry" respectively. The circle widths are directly proportional to the usage amount of the keywords, and the circle colors and the lines between the circles show the relationship status between the keywords (**Figure 4**).

While the institution citation network analysis was being conducted, 11 linked institutions from total 55 institutions that had at least 1 publication and cited at least once were included. The links between institutions are shown in **Figure 5**, and the width of the circles is proportional to the number of publications of the institutions. As a result of its numerous connections with other institutions, Harvard University appears to be at the top of the list in this field.

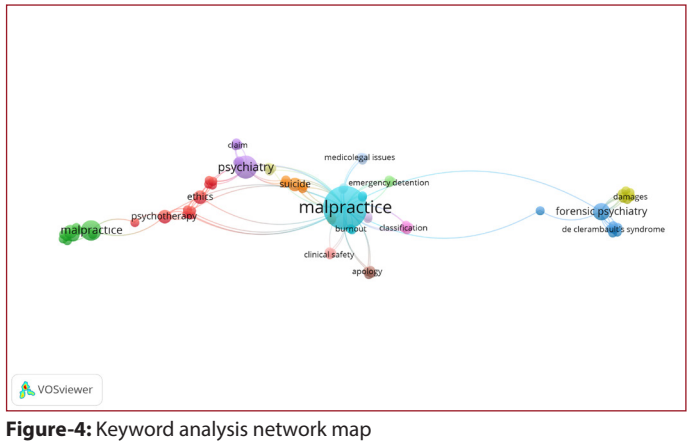

Figure-4: Keyword analysis network map

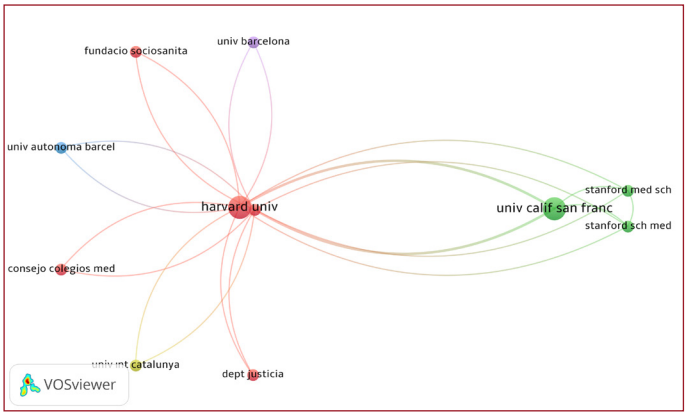

Figure-5: Institution citation analysis network map

Appelbaum PS and Gutheil TG were the most co-cited authors, according to the co-citation analysis in the context of authors. It was determined a total of 22 author clusters, and the authors with the strongest links were Black D, Gunderson JG, and Paris J.

All countries with at least 1 publication and at least 1 citation were included in the citation analysis in the context of countries, and it was determined that the country with the highest number of publications and citations was the United States, as seen in **Figure 6**. According to the number of citations and publications, other countries are Sweden, Spain, Italy, England, Turkey, and Romania respectively.

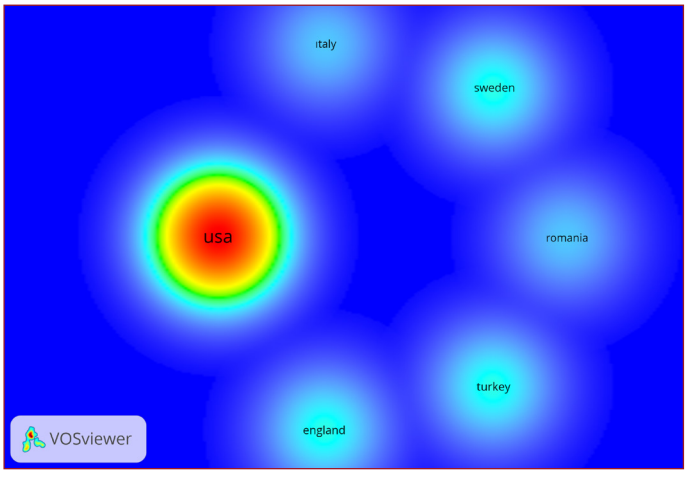

Figure-6: Citation analysis density image in the context of countries

DISCUSSION

In recent years, the increasing commercialization of the health system in almost all over the world has brought with it some negativities in terms of physicians and patients. In this respect, the subject of malpractice has become visible in all fields of medicine, but the boundaries of malpractice laws in many countries have not been clearly defined yet.[3] The topic of malpractice is on the research agenda for medical studies, yet there is not sufficient knowledge available, based on the literature data.[14] In the field of psychiatry, like other fields, there is not enough data on malpractice and clear legal regulations in most countries. While the society is protected by the rules on patient rights, legal regulations for physicians and other healthcare professionals are insufficient.[15] As a result of uncertainties in legal regulations and increased responsibilities, it is more and more common for physicians to face criminal liability.[14] It is known that the most common psychiatric malpractice cases are related to the patient's suicidal attempts, harming another person, misdiagnosis and wrong treatment practices, attempts to escape from the hospital, not obtaining informed consent, compulsory hospitalizations, and failure to protect confidentiality.[5]

In the results of our study, a total of 426 publications in the field of malpractice in psychiatry covering the years 1980-2022 were reached. It was observed that the number of publications was higher in the 2000s compared to the 1900s. The reason for this may be the commercialization of the healthcare system in recent years, the fact that patients have more information about their rights, they receive more healthcare services, and healthcare policies act to protect patients' rights rather than physicians.[16] The publications were mostly in the fields of psychiatry, government law, and psychology can be explained by the fact that the health professionals who are most interested in the subject work in these fields. The authors with the highest number of publications on psychiatry and malpractice are Scott C (2.5%) and Gutheil TG (2.3%) with 11 and 10 publications, respectively. It is possible to say that these authors are among the active authors interested in this field.

It was determined that the year with the highest number of publications on psychiatric malpractice was 2021. This can be explained by the fact that the COVID-19 pandemic has disrupted healthcare services and the issue has become more visible as patients resort to legal remedies. The relatively low number of publications in 2022 does not match the pandemic statement. Considering the number of publications in other years, it is seen that there is no regular increase or decrease. It has been determined that the number of publications is proportional to the number of citations, which is expected. Although the most common type of publication in this area is articles and reviews, the relatively low numbers explain the need for more studies in this area.

The institutions with the highest number of publications on psychiatric malpractice were Harvard University and Harvard Medical School. This can be explained by the presence of prominent and contemporary authors who deal with malpractice in these institutions. Journal of the American Academy of Psychiatry and the Law and American Journal of Psychiatry has the highest number of publications in this field may be related to the fact that this issue is more on the agenda in the United States.[17] When we evaluate the citation analyzes of the authors, the most cited authors were Adler NE, Moore PJ and Robertson PA, and it can be said that these authors made significant contributions to the related field. Another reason why these authors were cited in large numbers may be the fact

that the publications were made in a relatively old date, that is, the time advantage. The authors who have current publications on psychiatric malpractice are; Bekjord J, Bettinelli E, Mammen O, Painter T, and Tew J. When we examine the co-authorship analysis, the number of authors and the few connections are striking, and it can be said that the cooperation between researchers working on this subject is less than in other fields of medicine. The reason for this may be that the authors have different agendas in terms of malpractice, there is no possibility of cooperation and the number of researchers working on this subject is insufficient. Harvard University is seen to be at the forefront due to its multiple connections with other institutions can be explained by the tendency of the researchers working in this institution to cooperate with other institutions, the relatively high number of them and their strong communicative connections. The most frequently used keywords in research are malpractice, psychiatry and forensic psychiatry, respectively. This might be due to choosing the keywords for searches in this subject, those are the first words that come to mind. In the co-citation analysis, it was determined that the most co-cited authors were Appelbaum PS and Gutheil TG. This could be a result of that, these authors collaborate frequently and are some of the best-known authors in the area of psychiatric malpractice in terms of quantity and quality of publications. It is known that the book named Clinical Handbook of Psychiatry and the Law by these two authors is a guide for professionals working in this research area.[18]

In our study, a significant positive correlation was determined between the productivity of countries, their economic power and their level of development. As an expected result, this situation reveals once again that the issue of malpractice is more on the agenda in countries with high economic power and a high level of development. The United States is the most cited country in the citation analysis made in the context of countries can be explained by the high number of publications and their high quality. According to the number of citations and publications, other productive countries are Sweden, Spain, Italy, England, Turkey, and Romania. These findings show that the issue of psychiatric malpractice is also on the agenda in these countries and the authors' interest in this subject.[18-23] Other countries have limited number of publications compared to the United States. This may be related to the legal regulations in these countries, the lower number of malpractice cases, and the presence of fewer authors and institutions on this subject.[18,24,25]

Finally, some limitations of our research should be mentioned. Our analysis includes only the publications available from the Web of Science Core Collection database. Publications from other databases such as Scopus and PubMed are not included. Since our research is a bibliometric analysis study, it does not include detailed information on the contents of the publications and focuses mostly on quantitative data for the relevant research area.

CONCLUSION

In this study, it was seen that the publications in the field of psychiatry and malpractice were quite inadequate, the number of researchers working in this field and the connections between these researchers were weak. We believe that this results are important in terms of creating a research effect for the authors. With further investigations conducted on psychiatric malpractice, we hope that psychiatrists will be more informed on the subject so that errors resulting in legal consequences in this area would be decreased.

ETHICAL DECLARATIONS

Ethics Committee Approval: Since our research article is a bibliometric study, there is no need for an ethics committee approval.

Informed Consent: Since our research article is a bibliometric study, there is no need for an informed consent.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Ultrasonographic Measurement of Plantar Fascia Thickness in Patients with Hemiplegia

Hemiplejik Hastalarda Plantar Fasya Kalınlığının Ultrasonografik Değerlendirilmesi

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Abstract

Aim: In hemiplegic patients, changes in load distribution due to spasticity and paralysis cause trauma due to increased pressure and biomechanical problems in the plantar fascia on both sides. The aim of this study was to evaluate the plantar fascia thickness on both plegic and non-plegic sides by ultrasound in hemiplegic patients.

Material and Method: This cross-sectional study included patients with chronic hemiplegia (>6 months) and healthy control individuals. Clinical and demographic features were noted. Plantar fascia was visualized as hyperechoic fibrils by ultrasound. The thickness was measured in both sides and at one cm after the calcaneal connection.

Results: We included forty hemiplegic patients (22 males, 18 females) with a mean age of 58.60±11.8 years; and thirty-six age, sex, and body mass index (BMI) matched healthy subjects. Plantar fascia thickness values were significantly higher on the non-plegic side (3.82±0.1 mm) compared to that of plegic side (2.83±0.6 mm) and healthy groups sides (right side: 2.82±0,5; left side: 2.81±0,6) (p<0,001). There was no relationship found between plegic and healthy group sides (p>0,05). We also found significantly positive correlation between plantar fascia thickness of the non-plegic side and time since stroke (r=0.538, p<0.001) with tonus (r=0.378, p=0.016).

Conclusion: We can conclude that, plantar fascia thickness seems to be increased on the non-plegic side of patients.

Keywords: Plantar fascia, stroke, ultrasonography, walking disabilities.

Öz

Amaç: Hemiplejik hastalarda spastisite ve paralizi nedeniyle yük dağılımındaki değişiklikler bilateral plantar fasyada artan basınç ve biyomekanik problemlere bağlı travmaya neden olur. Bu çalışmanın amacı, hemiplejik hastalarda hem plejik hem de non-plejik taraftaki ve sağlıklı bireylerdeki plantar fasya kalınlığını ultrason ile değerlendirmektir.

Gereç ve Yöntem: Bu kesitsel çalışmaya kronik hemiplejili (>6 ay) hastalar ve sağlıklı bireyler dahil edildi. Klinik ve demografik özellikler not edildi. Plantar fasya ultrason ile hiperekoik fibriller olarak görüntülendi. Kalkaneal bağlantıdan 1 cm sonra hemiplejik hastalarda ve sağlıklı bireylerde bilateral plantar fasya kalınlıkları ölçüldü.

Bulgular: Ortalama yaşı 58.60±11.8 olan kırk hemiplejik hastayı (22 erkek, 18 kadın) ve yaş, cinsiyet ile vücut kitle indeksi (VKİ) uyumlu otuz altı sağlıklı bireyi dahil ettik. Plantar fasya kalınlık değerleri, plejik taraf (2.83±0.6 mm) ve sağlıklı gruplar (sağ taraf:2.82 ±0,50; sol taraf: 2.81± 0,6) ile karşılaştırıldığında non-plejik tarafta (3.82±0.1 mm) anlamlı olarak daha yüksekti (p<0,001). Plejik taraf ve sağlıklı grup plantar fasya kalınlığı değerleri arasında ilişki bulunmadı (p>0,05). Non-plejik tarafın plantar fasya kalınlığı ile inme sonrası geçen süre (r=0.538, p<0.001) ve tonus (r=0.378, p=0.016) arasında anlamlı pozitif korelasyon bulduk.

Sonuç: Hemiplejik hastaların non-plejik tarafında plantar fasya kalınlığının plejik taraf ve sağlıklı bireylere göre artmış olduğu sonucuna varabiliriz.

Anahtar Kelimeler: Plantar fasya, inme, ultrasonografi, yürüme bozuklukları.

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INTRODUCTION

In patients with post-stroke hemiparesis, spasticity, muscle weakness, abnormal muscle motor activity, abnormal muscle synergies, joint contractures, loss of proprioception and consequently mobility and gait disturbances are seen at different clinical levels. Muscle imbalance on the affected side often causes foot and ankle problems. Spasticity of plantar flexors or inverters and inadequate ankle dorsiflexion have been described following a stroke.[1] As a result, because only the forefoot touches the ground in the stance phase, there is no heel strike and the stance phase is shortened.[2] This increases the risk for muscle changes which affect the functional ambulation of walking and standing, and cause mechanical stress. The plantar fascia supports the middle part of the foot and joint metatarsophalanges. It provides stability at the end of the discharge phase and at the beginning of the release phase of gait.[3] Asymmetrical gait disturbances due to spasticity and paralysis are seen in stroke patients,[4] and these may cause increased pressure and biomechanical problems in both the plegic and the intact plantar fascia, and micro tears may also be seen in the plantar fascia.[5] If repeated excessive pressure is applied to the plantar fascia, it causes inflammation at the calcaneal attachment site and ultimately plantar fasciitis.[6] Although plantar fascia problems are common in patients after stroke, proper diagnosis and treatment is important. Ultrasonography has recently started to be used to evaluate the plantar fascia.[7]

To the best of our knowledge, there are few studies which have evaluated the plantar fascia with ultrasound in hemiplegic patients. Ultrasonography is easy to implement, inexpensive, does not expose the patient to ionizing radiation, is widely available, and is an imaging technique that allows for repeated measurements. Accordingly, the aim of this study was to evaluate the plantar fascia thickness using ultrasound on the plegic and non-plegic sides of hemiplegic patients.

MATERIAL AND METHOD

Study design and Participants

This cross-sectional study was conducted between August 2020 and October 2020. The plantar fascia thickness was measured using ultrasound in the plegic and non-plegic feet of ambulatory patients who were admitted to our outpatient clinic or hospitalized after stroke. The patients were selected consecutively.

The study included 40 chronic ischemic or hemorrhagic stroke patients (22 males and 18 females) with walking difficulties who were diagnosed with hemiplegia due to cerebrovascular event in the last 2 years. We also included healthy thirty-six (20 males and 16 females) individuals as a control group. Chronic stroke was defined as a 2-year period that started 6 months after stroke. Demographic and descriptive data such as age (years), gender (male or female), weight (kg), height (m) and lesion side (right or left), etiology, and disease duration were gathered.

A record was made for each patient of ankle joint range of motion and ankle tone, the Functional Ambulation Scale (FAS) score, use of a walking aid, and the presence of pain in the plantar fascia. The Ashworth Scale was used in the evaluation of hemiplegic tone.

Inclusion criteria were: (1) hemiplegic patients diagnosed with stroke at least 6 months prior to the study and (2) ability to walk. The exclusion criteria were defined as: (1) non-ambulatory patients, (2) the presence of ankle injury (fractures, sprains, tears in the post-stroke period) or tendinopathies (3) history of botulinum toxin injection to the gastro-soleus muscles (4) previous surgery in the lower extremities (5) fixed ankle contracture and (6) no cause for pes planus.

Approval for the study was granted by Hospital Ethics Committee (Date: 29.07.2020, Decision No: 1028) and the study was conducted in compliance with the Helsinki Declaration. All patients and the control group signed the informed consent form.

Ultrasound Assessment

The patients were positioned supine with the ankles in a neutral position. Care was taken to keep the ultrasound beam perpendicular to the plantar fascia to avoid anisotropy. The calcaneal attachment was visualized in the sagittal plane. The plantar fascia appears as a "linear fibrous hyperechoic band" against the background of a hypoechoic matrix.[8] The thickness of the plantar fascia was measured at the calcaneus insertion (**Figure 1**). Ultrasonographic examinations of all patients were performed by the same physician. The measurements were repeated thrice, and the average of the three values was used in the analysis. Ultrasonographic evaluations were applied using an ALOKA Prosound Alpha 6 (Hitachi Aloka Medical Systems, Tokyo, Japan) and the images were obtained with a 7.2 MHz linear array transducer.

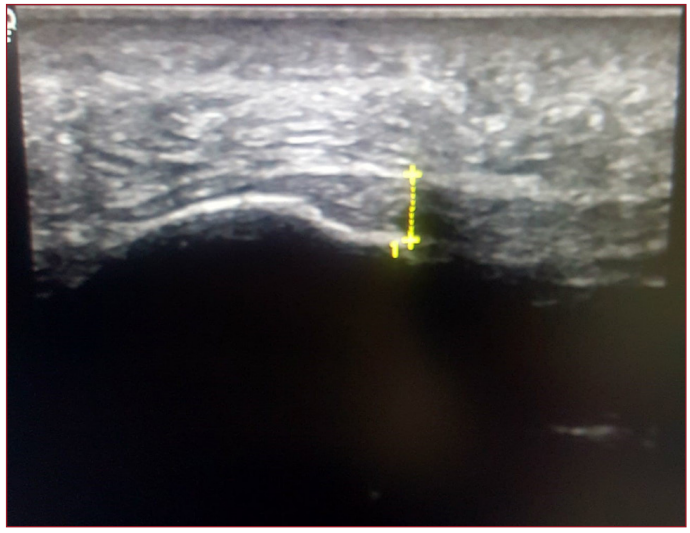

Figure 1. Sample image for the measurement of plantar fascia thickness
The plantar fascia is visualized as the hyperechoic fibrils.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS statistics for windows, version 21.0. (IBM Corporation, Armonk, NY, USA) software. Descriptive data were reported as mean±standard deviation (SD) values, number (n) and percentage (%). Conformity of the data to normal distribution was assessed with the Kolmogorov Smirnov Test and histograms. The Paired t-test and one-way analysis of variance were used to compare the plegic, non-plegic sides and healty group values. Pearson's correlation coefficient was used for analyzing correlation between Modified Ashworth Scale, FAS, duration of hemiplegia and the plantar facia thickness within groups. A value of p< 0.05 was accepted as statistically significant.

RESULTS

We enrolled forty consecutive chronic hemiplegia patients (22 males and 18 females) with a mean age of 58.60±11.8 years (range: 26-84 years), and thirty-six (20 males and 16 females) age, sex, and body mass index (BMI) matched healthy subjects (mean age: 57±12.5 years). Pain along the plantar fascia on the hemiplegia side was reported by 5 (12.5%) patients, and pain on the non-hemiplegia side by 12 (17.5%). The clinical and demographic characteristics of the patients are summarized in **Table 1**.

Table 1. Clinical and demographic characteristics

Variables	Hemiplegic Patients (n=40)	Healty group (n=36)	P value
Age (years)	58.60±11.8	57±12.5	NS
Gender			
Male, n(%)	22 (55)	20 (56)	
Female, n(%)	18 (45)	16 (44)	NS
BMI(kg/m^2)	28±4.2	27±3.4	NS
Time after stroke (months)	12 (8-24)	-	
Type of stroke			
Thromboembolic	35 (87.5)		
Hemorrhagic	5 (12.5)	-	
Hemiplegia Side			
Right	19 (47.5)		
Left	21 (52.5)	-	
Use of ambulation orthosis	22 (55)	-	
Functional ambulation category		-	
2	2 (5)		
3	10 (25)		
4	26 (65)		
5	2 (5)		
Modified Ashworth Scale		-	
0	7 (17.5)		
1/1+	9 (22.5)		
2	10 (25)		
3	14 (35)		
Range of Motion		-	
Normal	7 (17.5)		
Limited	33 (82.5)		

BMI= body mass index; NS=Non-significant

Plantar fascia thickness values were significantly higher on the non-plegic side (3.82±0.1 mm) compared to that of plegic side (2.83±0.6 mm) and healthy groups sides (right side:2.82±0.50; left side: 2.81±0.6) (p<0.001) (**Table 2**, **Figure 2**).

Table 2. Comparision of plantar facia thickness mesurements within groups

	Non-plegic side	Plegic side	Healthy group right side	Healthy group left side	P value
Plantar Facia Thickness (mm)	3.82±0.1[ab]	2.83±0.6[c]	2.82±0.5	2.81±0.6	<0.001

*P=ANOVA(ono-way analysis of variance), [a]p=0,001 versus hemiplegic side, [b]p=0,001 versus normal sides, [c]p>0,05 versus normal side

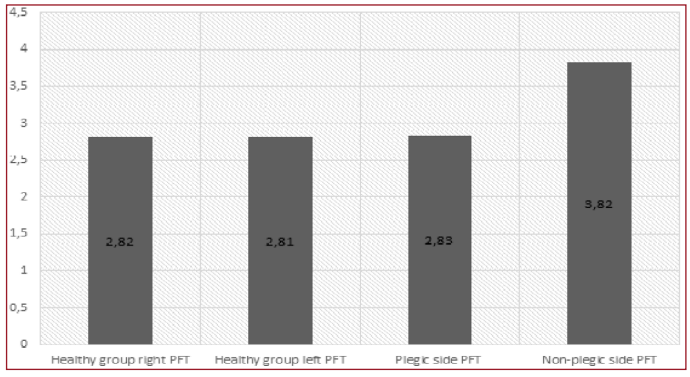

Figure 2. Plantar Fascia Thickness of the Healthy sides, Plegic side, Non-plegic Side

Plantar fascia thickness (PFT) values were significantly higher on the non-plegic side (3.82±0.1 mm) compared to that of plegic side (2.83±0.6 mm) and healthy sides (right side PFT:2.82±0,5; left side PFT: 2.81± 0.6). (p<0,001)

In the correlation analyses, a statistically significant positive correlation was determined between the plantar fascia thickness of the non-plegic side and the time since stroke (r=0.538, p<0.001) (**Figure 3**), and tonus (r=0.378, p=0.016) (**Figure 4**). As the tonus or time since stroke increased, so the plantar fascia thickness of the non-plegic side increased.

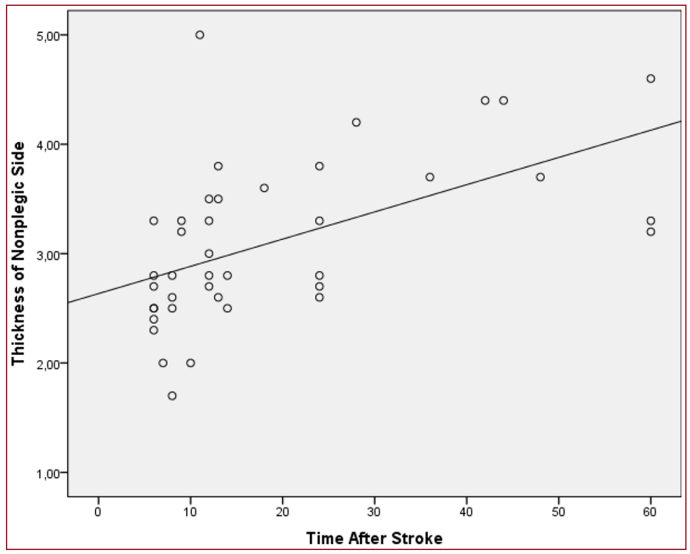

Figure 3. Plantar fascia thickness of the non-plegic side correlated significantly with the time since stroke (r=0.538, p<0.001). As the time since stroke increased, so plantar fascia thickness of the non-plegic side increased.

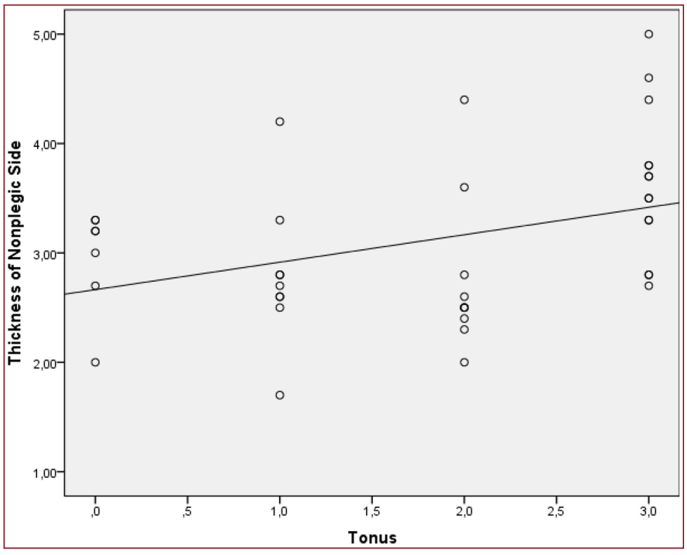

Figure 4. Plantar fascia thickness of the non-plegic side correlated significantly with tonus (r=0.378, p=0.016). As tonus increased, so plantar fascia thickness of the non-plegic side increased.

DISCUSSION

In this study, ultrasonography was used for plantar fascia thickness measurement in chronic stroke patients. According to the study results, it was concluded that chronic stroke patients have a thicker plantar fascia on the non-plegic side and that the plantar fascia thickness of the non-plegic side is significantly correlated with the time since stroke and tone.

The plantar fascia begins in the inner lump region of the calcaneus tubercle and includes the thick middle part and bilateral thinner parts.[9] In the histology of the plantar fascia, the extracellular matrix consists of collagen and elastic fiber, and spasticity causes changes in the alignment of elastic fibers induced by excessive pressure.[10] During ambulation, the plantar fascia plays an important role in supporting the plantar arch during the heel strike, full compression and thrust phases.[9] Therefore, it was thought that ambulation pathologies seen in hemiplegic patients may affect plantar fascia thickness. The study findings support this view, and there were thought to be several factors that could explain these findings.

Spasticity, muscle weakness, abnormal muscle motor activity, abnormal muscle synergies, joint contractures, loss of proprioception and consequently mobility and gait disturbances are seen at different clinical levels in stroke patients. While normal walking tends to be both spatially and temporally symmetrical, post-stroke gait is generally asymmetrical.[11,12] In patients with spastic hemiparesis, the center of foot pressure (CoP) shifts towards the non-plegic side when standing[13] and there is asymmetry in weight bearing.[14] In addition, the oscillation phase is longer than the normal, with prolonged single support time and double support time on the non-plegic side,[15,16] decreased step length on the plegic side, and shortened pressure time. Therefore, it is not easy to transfer body weight from the non-plegic side to the plegic side.[17] It can be considered that the thickness of the plantar fascia on the non-plegic side is affected in chronic stroke due to asymmetry in balance-load transfer.

Hemiplegic patients often have inadequate ankle dorsiflexion due to loss of motor control, spasticity of the gastrocnemius-soleus or invertor group, and / or ankle contracture.[18] These muscle changes affect functional ambulation, leading to an increased risk of mechanical stress on the foot when walking.[19] Spasticity and dynamic varus and plantar flexion deformation are common, especially in the plantar flexors of the ankle joint, which causes difficulties in supporting body weight.[20] In the current study, 35% of the patients had 3 points on the Ashworth Scale, and 25% had 2 points. Thus, the Ashworth Scale score of the spastic ankle was determined to be significantly correlated with the plantar fascia thickness of the non-plegic side.

Therefore, stretching and strengthening exercises for spastic muscles, botulinum toxin injections and solid ankle-foot orthoses in chronic stroke patients aim to stabilize the ankle in a neutral position and provide a more symmetrical and gait close to normal.

Plantar fascia problems in hemiplegic patients have been previously studied in the literature. Park Ji-won et al.[21] reported that plantar fascia thickness on the normal and plegic sides of stroke patients became statistically significant with the degree of spasticity, Riddle et al.[22] found that the risk of plantar fasciitis development was high in normal subjects due to the decrease in the degree of dorsiflexion of the ankle joint, and Irving et al.[23] reported that the decrease in ankle dorsiflexion ROM was significantly associated with the onset of plantar fasciitis. The current study was a cross-sectional ultrasonographic study. Ultrasound imaging equipment is useful for examining plantar fasciitis as it is non-invasive, easy-to-use, and changes in plantar fascia thickness can be easily and rapidly checked.[24,25]

These results were not consistent with those of a study by Tae-Gon Kim et al.[26] which showed that the plantar fascia thickness on the plegic and non-plegic side of the stroke patient group became statistically significant. In the current study, 12 patients had heel pain on the non-plegic side, and the modified Ashworth scale score was 3 in just over a third of the patients (35%). According to the functional ambulation scale, 30% of the patients were at a dependent level. The time since the stroke was 12 months on average (range, 8-24 months), and 55% of the patients used a walking aid or orthosis. In this study, the increase in tone on the plegic side of the patients, their being more dependent according to the FAS level, and the fact that patients with more acute episodes were included compared to similar studies, were interpreted as a change in plantar fascia thickness on the non-plegic side due to incomplete load transfer to the plegic side and the presence of asymmetrical walking.

While previous studies have focused on the plantar fascia content, in this study the function of the lower limb was evaluated with objective assessment on ultrasound of the thickness of the plantar fascia due to stiffness.

There were some limitations to this study, primarily the small sample size, lack of a control group and lack of more walking / functional parameters. In addition, that ultrasonography is user-dependent prevents generalization of the study results.

CONCLUSION

Chronic stroke patients have a thicker plantar fascia on the non-plegic side. In hemiplegic patients, the symmetry of weight transfer between plegic and non-plegic sides when standing and walking is important, and ambulation should be evaluated early in acute stroke patients. Specific treatment approaches based on symmetrical weight transfer between the sides of the body should be the primary focus in the early stages of rehabilitation. In addition, the management of changes in plantar fascia thickness is very important, and spasticity management is as important as treatment, as these changes are ultimately affected by spasticity. In the light of the findings of this study, it can be considered that the early initiation of conventional rehabilitation approaches, including spasticity therapy and balance load transfer, will be beneficial in the correction of foot biomechanics including plantar fascia disorders in hemiplegic patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adana City Training and Research Hospital Clinical Research Ethics Committee (Date: 29/07/2020, Decision No:1028).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Inflammatory Biomarkers and Echocardiographic Findings in Acute Rheumatic Fever Patients

Akut Romatizmal Ateş Hastalarında Yeni Biyomarkerler ve Ekokardiyografik Bulgular

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Abstract

Aim: Acute rheumatic fever (ARF) is an inflammatory disease that develops after Group A Streptococcal (GAS) tonsillopharyngitis in genetically susceptible individuals. We aimed to examine the clinical, laboratory, and echocardiographic findings of the patients diagnosed and followed up with ARF.

Material and Method: 55 patients under the age of 18 who were hospitalized and followed up with the diagnosis of ARF between January 2017 and January 2019 were included in this retrospective study. All cases were diagnosed with ARF according to the 2015 revised Jones criteria according to the intermediate-risk group. Gender, age, time of admission, physical examination findings, laboratory findings, echocardiographic findings, and data meeting major and minor diagnostic criteria of all patients diagnosed with ARF were recorded. Echocardiography and electrocardiography were performed on all patients. Inflammatory biomarkers were calculated using laboratory parameters. The data before the treatment and at the 8th week of the treatment were compared.

Results: 31 (56.4%) of the patients were female and 24 (43.6%) were male, the mean age was 13.70±2.44 years (7-18 years). The highest number of patients was in the 9-14 age group. The most frequent hospital admission season was winter. Arthritis and carditis were the most common major criteria. Post-treatment body weight, height, body mass index, and systolic and diastolic blood pressure values of the patients were statistically significantly higher than before treatment (p<0.001). The white blood cells (WBC), neutrophil (NE), monocyte (MO), eosinophil (EO), platelets (PLT), mean platelet volume (MPV), mean corpuscular hemoglobin concentration (MCHC), plateletcrit (PCT), C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Neutrophil-to-lymphocyte ratio (NLR), Neutrophil-to-monocyte ratio (NMO), and Systemic Inflammatory Index (SII) values decreased significantly after treatment. Before treatment, a moderate positive correlation was found between MPV and TLO (p: 0.045, r: -0.2712), MPV and LMO (p: 0.041, r: -0.2762), and a positive correlation at a moderate level between MPV and MPV/L (p: 0.001, r: 0.431). On the other hand, a high positive correlation was observed between SII and WBC (p: 0.001, r: 0.652), SII and NE (p: 0.001, r: 0.759), and SII and NLO (p: 0.001, r: 0.882) before treatment, while a moderate positive correlation was found between SII and TLO (p: 0.001, r: 0.598). Aortic valve regurgitation was significantly reduced with treatment. There was no significant difference in LVM and LVMI values after treatment (p:0.143, p: 0.672, respectively).

Conclusion: Our results suggests that there is no adverse effect on LV remodeling after treatment in patients with ARF. We believe that inflammation can be followed easily by using inflammatory parameters in the acute and post-treatment periods of the disease.

Keywords: Acute rheumatic fever, childhood, echocardiography, inflammation, rheumatic heart disease

Öz

Amaç: Akut romatizmal ateş (ARA) Grup A Streptokok (GAS) tonsillofarenjiti geçiren genetik olarak duyarlı bireylerde, enfeksiyonu takiben gelişen inflamatuvar bir hastalıktır. Bu çalışmada ARA tanısı ile takip edilen hastaların klinik, laboratuar ve ekokardiyografik bulgularının incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya Ocak 2017-Ocak 2019 tarihleri arasında 18 yaş altı ARA tanısı ile yatırılarak takip edilen 55 hasta dahil edildi. Tüm olgularda ARA tanısı 2015 yılı revize Jones kriterleri ile orta-risk grubuna göre konuldu. ARA tanısı konan tüm hastaların; cinsiyeti, yaşı, başvuru zamanı, fizik muayene bulguları, laboratuar bulguları, ekokardiyografi bulguları, major ve minör tanı kriterleri sağlayan verileri kaydedildi. Tüm hastalara ekokardiyografi ve elektrokardiyografi yapıldı. Laboratuvar parametreleri kullanarak inflamatuar biyobelirteçler hesaplandı. Tedavi öncesi ve tedavinin 8. haftasındaki veriler kıyaslandı.

Bulgular: Hastaların 31'i (%56,4) kız ve 24'ü (%43,6) erkek, yaş ortalaması 13,70±2,44 yıl (7-18 yıl) idi. En fazla hasta 9-14 yaş arasında görüldü. En sık hastaneye başvuru mevsimi kış idi. Major kriterlerden en sık kardit ve artrit görüldü. Hastaların tedavi sonrası vücut ağırlığı, vücut kitle indeksi, sistolik ve diyastolik kan basıncı değerleri tedavi öncesine göre istatistiksel olarak anlamlı yüksek bulundu (p<0,001). Beyaz kan hücreleri (WBC), nötrofil (NE), monosit (MO), eozinofil (EO), trombosit (PLT), ortalama trombosit hacmi (MPV), ortalama korpusküler hemoglobin konsantrasyonu (MCHC), trombositkrit (PCT), C-reaktif protein (CRP), Eritrosit Sedimentasyon Hızı (ESR), Nötrofil-lenfosit oranı (NLR), Nötrofil-monosit oranı (NMO) ve Sistemik İnflamatuar İndeks (SII) değerleri tedaviden sonra önemli ölçüde azalmış bulundu. MCH, RDW, PDW, L/CRP değerleri tedavi sonrasında anlamlı olarak artmıştı. Hastaların tedavi öncesi MPV ile TLO (p: 0,045, r: -0,2712), MPV ile LMO (p: 0,041, r: -0,2762), MPV ile MPV/L arasında pozitif yönde orta (p: 0,001, r: 0,431) düzeyde korelasyon saptanırken; tedavi öncesi SII ile WBC (p: 0,001, r: 0,652), SII ile NE (p: 0,001, r: 0,759) ve SII ile NLO arasında pozitif yönde yüksek (p: 0,001, r: 0,882) korelasyon, SII ile TLO arasında ise pozitif yönde orta (p: 0,001, r: 0,598) düzeyde korelasyon olduğu tespit edilmiştir. Tedavi ile aort kapak yetmezliğinin anlamlı olarak azalmış olduğu gösterildi. Tedavi sonrasında LVM ve LVMI değerlerinde ise anlamlı fark tespit edilmedi (sırasıyla p:0,143, p: 0,672).

Sonuç: Çalışmamızdaki hastaların klinik bulgularının sıklığı literatürle benzerdir. ARA'lı hastalarda tedavi sonrası LV remodeling üzerinde olumsuz etki olmadığını düşündürmektedir. Hastalığın akut ve tedavi sonrası sürecinde inflamatuar parametreler kullanılarak inflamasyon takibinin kolaylıkla yapılabileceğini düşünmekteyiz.

Anahtar Kelimeler: Akut romatizmal ateş, çocukluk çağı, ekokardiyografi, romatizmal kalp hastalığı

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INTRODUCTION

Acute rheumatic fever (ARF) is an inflammatory disease that affects the joints, heart, brain and skin, resulting from an abnormal immune response to Group A Streptococcal (GAS) infection.[1] In genetically susceptible individuals, after an average of three weeks latent period from GAS tonsilopharyngitis, a nonsuppurative, multisystemic, inflammatory connective tissue disease that causes rheumatic heart disease occurs as a result of widespread systemic involvement in the heart, joints, and brain, and damage to the collagen fibers and heart valves of the connective tissue.[1] While the incidence and importance of acute rheumatic fever (ARF), which is still an important public health problem, is decreasing in developed countries, its importance continues in developing countries.[2] In developed countries, the incidence of the disease has decreased in recent years thanks to the gradual improvement of living conditions, early detection of the disease, timely and appropriate start of antibiotic treatment and prophylaxis, public awareness, close follow-up of patients, and the use of non-invasive diagnostic methods such as echocardiography (ECHO).[3]

ARF is one of the leading causes of acquired heart disease in the pediatric age group worldwide.[3] ARF is more common in children aged 5-15 years.[4] Globally, it is estimated that approximately 500,000 new cases of ARF are diagnosed annually and approximately 230,000 people die from the disease each year. ARF is among the leading causes of cardiovascular death in the first 50 years of life.[5]

The diagnosis of ARF is made using the updated Jones criteria consisting of clinical and laboratory findings, as reported by the American Heart Association (AHA) in 2015.[6] Since the frequency of the disease shows a heterogeneous course in the world and the risk situation changes accordingly, it is thought that a single diagnostic criterion will not be sufficient when diagnosing in all societies, diagnostic criteria have been arranged according to two different groups as risky in order to prevent misdiagnosis in regions where the disease is rare and not to miss a diagnosis in regions where the incidence of the disease is high.[6] The incidence of ARF varies in Turkey, in regions and even in different provinces of the same regions. According to a recent study, the estimated incidence rate of ARF was reported as 8.84/100 000 in Turkey.[7]

We aimed to examine the clinical, echocardiographic and laboratory findings of the patients diagnosed with ARF and followed up in this study.

MATERIAL AND METHOD

This retrospective study was conducted in patients hospitalized with the diagnosis of ARF between January 2017 and January 2019. Necessary permissions were obtained for the protocol of the study, and the Selcuk University Local Ethic Committee was approved the study (approval number: 2019/321, approval date: 13.11.2019).

A total of 55 patients under the age of 18 who were hospitalized and followed up with the diagnosis of ARF were included in the study. The clinical, laboratory and echocardiographic findings of the patients were compared before and after the treatment. We also examined the relationship between new inflammatory markers and acute phase reactants and hematological parameters. In all cases, the diagnosis of ARF was made according to the 2015 revised Jones criteria according to the medium-high risk group 6.

Gender, age, time of admission, physical examination findings, laboratory findings, echocardiographic findings, and major and minor criteria of all patients diagnosed with ARF were recorded. The patient's fever, arthritis (monoarthritis, polyarthritis), cardiovascular system examination (tachycardia, murmur), ECG findings, erythema marginatum, subcutaneous nodule, Sydenham chorea were also recorded from the patient file records. BMI was calculated with the formula weight (kg)/height (m^2). After resting for 5 minutes, systolic and diastolic blood pressures were measured with a cuff suitable for the patient's arm at heart level. ECG findings were interpreted by a same, single pediatric cardiologist.

ECHO examination was performed with the Philips EPIQ 7C (USA) device, by taking multiple orthogonal parasternal, apical and subcostal images of the patients lying in the left lateral decubitus position by the same pediatric cardiologist. Traditional ECHO evaluation includes measurements of LV end-diastolic and end-systolic diameter, septal and LV posterior wall thicknesses in diastole and systole, LV ejection fraction (EF) and LV fractional shortening (FS) from the parasternal long-axis view. EF and FS were calculated using Teichholz's M-mod formula. Left ventricular mass calculated by the formula developed by Devereux et al.[8]:

$$\mathbf{LVM=0.8\{1.04[LVIDD+İVS(d)+LVPWD(d))^3-(LVIDD)^3]\}+0.6}$$

The left ventricular mass index was calculated by dividing the LVM length by the 2.7 strength (m2.7).

Laboratory Parameters

Autoanalyzer was used on Beckman Coulter DXH 800 and Beckman Immage 800 devices. Inflammation parameters were neutrophil lymphocyte ratio (NLR) which calculated as peripheral blood neutrophil count divided by total lymphocyte count, platelet lymphocyte ratio (PLR) which calculated as platelet count divided by lymphocyte count, lymphocyte monocyte ratio (LMR) which calculated as lymphocyte count divided by monocyte count, neutrophil monocyte ratio (NMO) which calculated as neutrophil count divided by monocyte count, lymphocyte CRP ratio (L/CRP) which calculated as lymphocyte count divided by CRP value, MPV lymphocyte ratio (MPV/L) which calculated as MPV value divided by lymphocyte count, and Systemic Inflammatory Index (SII) which calculated as dividing the platelet count x neutrophil count/lymphocyte count.

The data before the treatment and at the 8th week of the treatment were compared. Aspirin 75-80 mg/kg/day in 4

doses was given to 4 patients diagnosed with isolated arthritis and mild carditis, naproxen was given in 2 doses of 15 mg/kg/day to 2 patients with isolated arthritis, and prednisolone 2mg/kg/day was given in divided doses to 49 patients with moderate and severe carditis. Absolute bed rest was started. Serial ECO was performed at regular intervals. All patients were given secondary prophylaxis and patients with valve findings were given infective endocarditis prophylaxis.

Statistical Analysis

All data obtained from patient files, examination findings and laboratory parameters, and cardiological evaluation findings were recorded in the dataset. These recorded data were analyzed with the Statistical Analysis for Social Sciences (SPSS) package program version 23.0. Conformity to normal distribution was evaluated with the Shapiro Wilk test. Normally distributed data were presented as mean ± standard deviation. Data that did not show normal distribution were shown as median (minimum-maximum). Categorical data were presented as frequency % (percent). Chi-square test was used to compare categorical data. The relationship between continuous variables was examined by correlation analysis. In the comparisons before and after the treatment, the data suitable for normal distribution were analyzed with the paired-t test, and the data not suitable for the normal distribution were analyzed with the Wilcoxon test. The McNemar test was used to compare bi-state categorical variables before and after treatment. Values of categorical data were presented with bar and pie charts. For statistical significance level, $p<0.05$ was accepted. All analyzes were performed by an experienced statistician.

RESULTS

A total of 55 patients included in the study, 31 (56.4%) were female and 24 (43.6%) were male, and the female/male ratio was 1.29. The mean age of patients with ARF was 13.70±2.44 years. The median age of the patients was 13.50 years, while the youngest patient was 7 years old, and the oldest patient was 18 years old. There was no statistically significant difference in terms of mean age according to gender ($p>0.05$). The most ARF patients were between the ages of 9-14. No patients under the age of five were identified. Considering the season of admission of the patients to the hospital, it was most common in winter with 30 (54.5%) patients. The season of admission to the hospital was most common in winter with 30 patients (54.5%).

Body weight, body mass index, systolic and diastolic blood pressure values of the patients included in the study were statistically significantly higher after treatment compared to before treatment ($p <0.001$).

The most common ARF major criteria in our patients were carditis (89%) and arthritis (76.3%). Considering the rates of single and coexistence of the major criteria, isolated arthritis in 4 patients (7.2%), isolated carditis in 6 patients (11%), carditis and chorea in 7 patients (12.7%), arthritis and carditis in 30 patients (54%, 5), arthritis, carditis and erythema marginatum in 2 patients (3.6%), arthritis, carditis and subcutaneous nodule in 1 patient (1.8%), polyarthralgia in 2 patients (without arthritis), polyarthralgia in 3 patients (3.6%) and coexistence of polyarthralgia and carditis were reported in 3 patients (3.6%). Polyarthritis was determined in 24 (57%) of 42 patients with major joint findings, monoarthritis in 13 (31%) and polyarthralgia (without arthritis) in 5 (12%) patients (**Table 1**).

Table 1. Distribution of major findings of patients in the medium-high risk group according to "2015 revised Jones criteria"

Major Criteria	All Patients (n: 55)	
	Number (n)	Frequency (%)
Arthritis/Polyarthralgia	42	76.3
Carditis	49	89
Rheumatic Chorea	7	12.73
Erythema Marginatum	2	3.6
Subcutaneous Nodule	1	1.82

When the patients diagnosed with ARF were examined according to minor criteria, 54 (98.18%) of the patients had elevated ESR, 45 (81.81%) of patients had elevated CRP, 15 (27.27%) patients had monoarthralgia, 4 (7%, 27) patients had PR prolongation, and fever were determined in 2 (3.6%) patients (**Table 2**).

Table 2. Distribution of minor findings of patients in the moderate-high risk group according to "2015 revised Jones criteria"

Minor criteria	All Patients (n: 55)	
	Number (n)	Frequency (%)
Monoarthralgia	15	27.27
Elevated CRP	45	81.81
Elevated ESR	54	98.18
Prolonged PR	4	7.27
Fever	2	3.6

Abbreviations: CRP: C-reactive Protein, ESR: Erythrocyte Sedimentation Rate, PR: P-R distance in electrocardiography

Considering the positivity rates of CRP elevation, ESR elevation, and PR prolongation before and after treatment, which are minor criteria, CRP elevation was present in 81.8% of patients before treatment, while this rate decreased to 16.3% after treatment. Similarly, the rate of elevated ESR decreased from 98.1% to 16.4%. While PR prolongation was detected in 7.3% of patients before treatment, this rate decreased to 0% after treatment, that is, PR prolongation was not observed in any patient (**Table 3**).

Table 3. Distribution of minor criteria before and after treatment

Minor criteria		Number (n)	Frequency (%)
Elevated CRP	Pre-treatment	45	81.8
	Post-treatment	9	16.3
Elevated ESR	Pre-treatment	54	98.1
	Post-treatment	9	16.4
Prolonged PR	Pre-treatment	4	7.3
	Post-treatment	0	0

Abbreviations: CRP: C-reactive Protein, ESR: Erythrocyte Sedimentation Rate, PR: P-R distance in electrocardiography

When the patients diagnosed with ARF were examined according to the supportive findings, ASO elevation was detected in 48 (87.27%) and AGBHS was found to be grown in 2 (6%) of 33 patients who had a throat culture. Aortic valve insufficiency was detected in 41 patients before treatment in ARF patients while it was detected in 26 patients after treatment. Post-treatment recovery rate of patients with aortic valve insufficiency was 36.6%. There was a statistically significant difference between before and after treatment in terms of the presence of aortic valve insufficiency (p:<0.001). Mitral valve insufficiency was present in 49 patients before treatment in ARF patients while it was detected in 46 patients after treatment. There was no statistically significant difference between pre- and post-treatment in terms of the presence of mitral valve insufficiency (p: 0.250)

In our study, when the laboratory values of the patients were examined according to the treatment, a statistically significant difference was found in the hemogram parameters of WBC, PLT, MCV, MCH, MPV, NE, MO, RDW, PDW, PCT, MCHC, EO compared before and after treatment. WBC, PLT, MPV, NE, PCT, MCHC, MO values decreased significantly after treatment, while MCH, RDW, PDW values increased significantly after treatment (**Table 4**).

In our study, when the laboratory values of the patients were examined according to the treatment, a statistically significant difference was found when the CRP, ESR, NLR, TLR, NMO, L/CRP, SII were compared before and after the treatment. CRP, ESH, NLR, NMO, TLR, EO, and SII values decreased significantly after treatment, whereas L/CRP values increased significantly after treatment (**Table 5**).

When the echocardiographic examination results before and after treatment in ARF patients were compared, a decrease in LVIDd and an increase in EF were statistically significant after treatment. No significant difference was found in the evaluation of LVM and LVMI (**Table 6**).

Table 4. Hemogram values of ARF patients before and after treatment

	Pre-Treatment		Post-Treatment		P values
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
WBC (10^3/µl)	15.63±6.22	14.2 (6.5 - 34.5)	10.82±3.13	10.2 (6.3 - 20.7)	<0.001
HGB (g/dL)	13.2±1.41	13.4 (9.9 - 15.8)	13.51±0.93	13.5 (11.7 - 15.3)	0.129
HCT (%)	40.14±4.5	40.2 (30 - 49.1)	40.63±2.82	40.6 (34.2 - 46.5)	0.445
PLT (10^3/µl)	428.11±118.98	415 (220 - 779)	305.11±111.06	271 (160 - 612)	<0.001
MCV (fL)	80.33±5.1	80.1 (70 - 100)	81.45±5.03	81.3 (68.7 - 98.8)	<0.001
MCH (pg)	26.37±1.82	26.3 (22.8 - 34)	27.19±2.00	27.4 (23.2 – 33.6)	<0.001
MPV (fL)	7.68±0.93	7.7 (6.1 - 10.7)	7.44±0.86	7.5 (6 - 9.7)	0.005
NE (10^3/µl)	11.83±5.75	10.6 (3.7 - 28)	6.87±2.89	6.8 (2 - 15)	<0.001
LY (10^3/µl)	2.71±0.84	2.6 (1.14 - 4.9)	2.79±0.91	2.7 (1.2 - 6.2)	0.670
RDW (%)	14.92±2	14.4 (12.3 - 24)	17.69±2.61	17.4 (12.9 - 24.4)	<0.001
PDW (fL)	16.36±0.61	16.3 (15.4 - 18.6)	16.63±0.66	16.6 (13.9 - 17.9)	<0.001
PCT (%)	0.31±0.09	0.3 (0.16 - 0.61)	0.22±0.08	0.19 (0.12 - 0.46)	<0.001
MCHC (g/dL)	32.76±1.09	32.8 (26.6 - 34.2)	27.19±2.01	27.4 (23.2 - 33.6)	<0.001
EO (10^3/µl)	0.11±0.35	0.02 (0 - 2.31)	0.13±0.31	0.05 (0 - 2.1)	<0.001
BA (10^3/µl)	0.05±0.06	0.03 (0 - 0.34)	0.05±0.12	0.03 (0 - 0.8)	0.355
MO (10^3/µl)	1.01±0.5	0.93 (0.17 - 2.26)	0.84±0.33	0.78 (0.4 - 1.9)	<0.001

Abbreviations: WBC: white blood cell count, Hgb: Hemoglobin, HCT: hematocrit, PLT: Platelet count, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MPV: Mean platelet volume, NE: Neutrophil, LY: Lymphocyte, RDW: Erythrocytes distribution width, PDW: Platelet distribution width, PCT: Mean platelet percentage, MCHC: Mean cell hemoglobin concentration, EO: Eosinophil, BA: Basophil, MO: Monocyte

Table 5. Comparison of inflammation parameters before and after treatment in ARF patients

	Pre-Treatment		Post-Treatment		P values
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
CRP (mg/L)	53.52±63.21	18 (0.4 - 235)	4.52±5.71	2.21 (0.1 - 27)	<0.001
ESR (mm/hour)	59.73±22.46	57 (13-119)	11.95±8.21	11 (2 - 33)	<0.001
N/L ratio	4.57±2.42	4.23 (0.87-11.25)	2.76±1.62	2.21 (0.52 - 8.07)	<0.001
Plt/L ratio	169.75±82.35	158 (16 - 501)	122.47±60.72	103 (35.3 - 344)	<0.001
L/M ratio	3.45±1.97	2.8 (1.2 - 9.75)	3.62±1.32	3.7 (1 - 7.75)	0.149
N/M ratio	13.74±9.58	11.96 (2.91 - 65.29)	8.83±4.15	8.36 (2.86 - 28.25)	<0.001
L/CRP ratio	0.63±1.28	0.14 (0.01 - 6.5)	4.14±9.85	1.04 (0.12 - 62)	<0.001
MPV/L ratio	3.16±1.2	2.96 (1.61 - 6.62)	2.96±1.1	2.72 (1.23 - 8.08)	0.346
SII	2050.16±1566.63	1713.8 (361.05- 8763.75)	837.68±581	566.5 (195.8- 2827.2)	<0.001

Abbreviations: CRP: C-reactive protein, ESH: Sedimentation, N/L: Neutrophil Lymphocyte ratio, T/L: Platelet Lymphocyte ratio, L/M: Lymphocyte Monocyte ratio, N/M: Neutrophil Monocyte ratio, L/CRP: Lymphocyte CRP, MPV/L: Mean Platelet volume Lymphocyte ratio, SII: Systemic Inflammatory Index

Table 6. Comparison of echocardiographic parameters of ARF patients before and after treatment

	Pre-Treatment		Post-Treatment		P values
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
İVSd (mm)	7.54±1.31	7.7 (4 - 10)	7.87±1.11	8 (5 - 11)	0.119
LVIDd (mm)	38.54±7.77	39 (5.5 - 50.2)	38.01±5.14	38.4 (23.5 - 47.6)	0.008
LVPWd (mm)	8.12±4.11	7.6 (5 - 36.5)	7.91±2.31	7.7 (5 - 21)	0.459
İVSs (mm)	9.07±2.1	8.8 (6.1 - 21)	8.85±1.18	9 (6.1 - 11)	0.508
LVIDs (mm)	23.67±4.25	23.6 (9.6 - 40)	22.94±5.46	22.9 (8.3 - 39.6)	0.238
LVPWs (mm)	9.73±2.31	9.6 (6 - 21.8)	9.5±2.26	9.2 (6.1 - 22)	0.439
EF (%)	70.6±4.47	71 (63 - 79)	72.28±4.16	72 (65 - 80)	0.040
FS (%)	39.8±3.91	40 (34 - 49)	40.72±4	40 (33 - 53)	0.223
LVM (g)	93.34±36.78	85.07 (0.6-193.42)	101.25±47.93	91.66 (8.17-346.95)	0.143
LVMI (g/m2,7)	37.87±16.63	36.43 (0.19 - 86.02)	35.92±14.92	34.53 (2.59 – 101)	0.672

Abbreviations: IVSd: Interventricular septum in diastole, LVPWd: Left ventricular posterior wall thickness in diastole, LVIDd: Left ventricular end-diastolic diameter, IVSs: Interventricular septum in systole LVIDs: Left ventricular end-systolic diameter, LVPWs: Systole left ventricular posterior wall thickness EF: Ejection fraction, FS: Fractional shortening, LVM: Left ventricular mass, LVMI: Left ventricular mass index

The correlation between pre- and post-treatment hemogram and inflammation parameter values and MPV was investigated. Accordingly, it was determined that there was a weak negative correlation between MPV before treatment and TLR, LMO, and CRP after treatment, a moderate positive correlation between MPV/L, a positive high correlation between pretreatment SII and WBC, NLR, NE, and a moderate positive correlation between TLR. No correlation was found between SII and pre- and post-treatment ESR, and CRP.

DISCUSSION

In this retrospective study, clinical, laboratory and echocardiographic features of patients hospitalized with the diagnosis of ARF before and after treatment were examined. Inflammatory parameters were also studied.

The mean age of ARF patients in our study was 13.70±2.44 years. The oldest of the patients was 18 years old and the youngest was 7 years old. When the cases were classified according to age groups, the most patients were between the ages of 9-14 and constituted 58.1% of all cases. We did not have any patients under the age of five, 1 (1.9%) between the ages of 5 and 8, and 22 (40%) patients over the age of 15 were identified. In the study of Ozer et al., which included 129 children with ARF in 1999-2000, the mean age of the patients was 11.2 ± 2.73 years, Boyarchuk et al. found 10.5 ± 1.85 years, and Gurses et al. determined the mean age as 11±2.8 years. [9-11] In a study conducted in Israel between 2000 and 2005, it was reported that 79.5% of the patients were in the 5-14 age group, 16% were over the age of 15, and 4.5% were between the ages of 25-29.[12] In a retrospective study of 1103 patients in Turkey in 2021, the mean age of ARF patients was reported as 11 ± 2.7 years. Studies conducted in India, Australia and Aborigines show similarities with the literature.[13,14] In this context, the mean age of the patients we examined in our study is consistent with the literature.

The incidence of ARF is equal in boys and girls.[15] In the study of Gungor et al. in 2014, 46.5% of the patients were female and 53.5% were male.[16] In a multicenter study conducted in 2021, the male/female ratio was reported as 1.09 . In our study, 31 (56.3%) of the patients diagnosed with ARF were female and 24 (43.6%) were male. The female to male ratio was 1.29. In our study, the rate of female gender was higher in patients diagnosed with ARF, but the difference was not statistically significant.

Since throat infections due to GAS are most common in spring and winter, ARF is most common in these seasons.[17] In our study, 30 (54.5%) of the patients were applied in winter, 13 (23.6%) were applied in summer, 11 (20%) were applied in spring, and 1 (1.8%) were applied in autumn, according to the order of admission season. This result suggests that GAS infection may cause ARF not only in winter but also in other seasons in susceptible individuals.

In our study, when the major criteria during the acute attack of 55 patients with ARF were examined, isolated arthritis in 4 patients (7.2%), isolated carditis in 6 patients (11%), carditis and chorea in 7 patients (12.7%), arthritis and carditis in 30 patient (54.5%), arthritis, carditis and erythema marginatum in 2 patients (3.6%), arthritis, carditis and subcutaneous nodule in 1 patient (1.8%), polyarthralgia in 2 patients (without arthritis) (% Polyarthralgia and carditis were found together in 3, 6 and 3 patients (5,4%). Considering the rates of major criteria in ARF, carditis was reported 30-70%, arthritis 40-70%, chorea 10-30%, erythema marginatum below 5%, and subcutaneous nodule 0-10%.[17] In the study by Carapetis et al. and in Australia, carditis was 55%, arthritis 55%, chorea 28%, erythema marginatum 0.5% and subcutaneous nodule 0.5%, in a study conducted in Ukraine in 2017 with the participation of 85 centers. In the study, carditis was reported 84.7%, polyarthritis 54.7%, chorea 25.9%, subcutaneous nodule 8.2%, erythema marginatum 5.9%.[18] In a recent multicenter study, arthritis (52.8%), carditis (53.5%), chorea (7.9%), erythema marginatum (0.36%) were observed, and no subcutaneous nodule was observed.[19] The incidence of major criteria for ARF in our study is similar to the literature.

Among the minor findings, ESR elevation was reported in 81.8%-95%, arthralgia 54.6%-81.1%, fever 40-62%, PR interval prolongation 15.8%-23%, and CRP elevation was reported in 72-81.8% of ARF patients.[20] In the retrospective studies of

Orun et al. from our country between 1980 and 2009, it was reported that CRP elevation was in 71.2%, ESR elevation was in 87.3%, fever 41.5%, arthralgia 60.6%, and PR prolongation was found in 15.8% of ARF patients.[21] PR prolongation was found in 20% of the patients in the study of Karacan et al. and in 23% of the patients in the study of Alqanatihs et al.[22,23] In the study conducted by Gungor et al. in 2004-2009, fever (28%), arthralgia (20.6%), PR prolongation (15.2%), ESR elevation (97.5%) and CRP elevation (84.9%) were reported.[16] In the national 2021 study, fever was reported in 33%, prolonged PR interval in 13.2%, monoarthralgia in 1.6%, elevated ESR in 80%, and elevated CRP in 77% of ARF patients.[19] ESR and CRP, which are acute phase reactants, are non-specific parameters for acute rheumatic fever. ESR and CRP are typically elevated in patients with ARF. It is important in monitoring the acute phase of ARF. Of the patients included in our study, 39 (70.91%) had elevated CRP, 54 (98.18%) elevated ESR, 2 (3.6%) had fever, 4 (7.27%) had PR prolongation according to age and heart rate, and monoarthralgia were observed in 15 (27.27%) patients. These findings appear to be comparable to previous studies.

Supporting findings are data proving previous streptococcal infection. The most common supportive laboratory finding is high ASO.[24] In terms of supporting findings in our study, ASO titer was elevated in 48 patients (87.27%), and GAS was observed in 2 (6%) of 33 patients whose throat cultures were taken. The rate of cases with high ASO was similar to the literature. The low positivity in the throat culture of the patients is thought to be related to their previous use of antibiotics due to upper respiratory tract infections.

Echocardiographic examination has been of great importance for years in the diagnosis, treatment response and long-term follow-up of acute rheumatic fever. It is a frequently used diagnostic method because it is non-invasive, accessible, and practical. EF and FS measurements are standard methods for evaluating left ventricular systolic function. The diagnosis of subclinical carditis is also accepted as a major finding in the 2015 updated Jones criteria. Echocardiography plays a major role in the diagnosis of subclinical carditis in patients without a murmur on auscultation.[6] The relationship between corticosteroid and myocardial hypertrophy was first described by Alpert in a 14-month-old patient, and it was observed that cardiac pathology regressed, and ECHO findings returned to normal with steroid reduction.[25] Miranda-Mallea et al., on the other hand, reported that corticosteroids can cause hypertension, and hypertension results in hypertrophy directly in the heart muscle.[26] There has been a direct correlation between aldosterone levels and LVM in patients with chronic renal failure.[27] LVM and LVMI have not been previously studied in ARF patients in the literature. In our study, no significant difference was found when LVM and LVMI were compared before and after treatment. Our findings suggest that steroid therapy does not have a negative effect on cardiac remodeling in the early period in patients with ARF.

Hemogram, inflammation parameters and rates have been evaluated by studies conducted in various diseases over time, as well as their routine use.[28] In a study by Sert et al., which included 40 patients and 40 healthy groups, there was no significant difference between the two groups in terms of platelet and MPV values, while there was a significant increase in WBC counts when the patients with ARF were compared after diagnosis and treatment.[19] Compared to the healthy control group, a statistically significant increase in WBC and platelet counts, and a significant decrease in MPV values were found in the acute attack of patients with ARF.[19] In their study, Sert et al. reported that the decrease in MPV value in ARF patients in acute attack caused the inhibition of megakaryopoiesis as a result of excessive production of proinflammatory cytokines and acute phase reactants, and this caused the release of small-sized platelets from the bone marrow.[19] Previously reported studies have shown that IL-6 causes an increase in platelet count and a decrease in MPV values.[29] In a study conducted by Aşık et al., in which 50 patients with ARF and 50 control groups participated, a statistically significant difference was found, with WBC, neutrophil count, neutrophil/lymphocyte count ratio, and platelet high in the case group, while lymphocyte, hemoglobin, and MPV were high in the control group.[30]

In the literature, SII and L/CRP has not yet been studied in patients with ARF. In our study, when the laboratory values of the patients were examined, it was determined that WBC, PLT, MPV, NE, PCT, MCHC, MO, CRP, ESH, NLR, NMO, TLO, EO, and SII values decreased significantly after treatment, while MCH, RDW, PDW, L/CRP values increased significantly after treatment.

When the studies on the correlation analysis of acute phase values of ARF patients were examined, it was seen that there was a correlation between the neutrophil/lymphocyte ratio and WBC, sedimentation, and CRP values in the ARF study of Çelik et al.[31] On the other hand, Giray et al. reported a positive correlation between platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio and ESH and CRP values.[32] In their study, Sert et al. reported a negative correlation between ESR, WBC, MPV and PLT in the correlation analysis of acute phase values before treatment.[19]

In our study, the correlations between pre- and post-treatment values of hemogram and inflammation parameters and MPV, SII were examined. Pre-treatment MPV and pre-treatment TLR, LMO, pre-treatment MPV and post-treatment CRP were negatively weak, MPV/L positively moderate, pre-treatment SII and WBC, NLR, NE were positively high, TLR was moderately positive correlation was determined. We believe that these parameters, which are simple, applicable and easily accessible, may be useful for the follow-up of inflammation in ARF.

Limitations

Due to the retrospective nature of our study, there are certain limitations. Limitations such as the fact that patient data

were obtained from the file records and the patients received different treatments may also have affected our results. The accuracy of our findings can be confirmed by examining more patients in larger studies in the future. Despite these limitations, we believe that our study will contribute to the literature thanks to its previously unpublished findings.

CONCLUSION

The clinical findings of our ARF patients are comparable to the literature data. In our study, there was no significant change in LVM and LVMI values before and after treatment, and we believe that LV remodeling was not affected by treatment. We showed that aortic valve regurgitation was significantly reduced with treatment. Significant changes in inflammatory parameters such as L/CRP after treatment, a positive high correlation between pretreatment SII and WBC, NLR, NE, and a moderate positive correlation between TLR may be an easy and applicable option for the evaluation of inflammation in ARF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selcuk University Local Ethic Committee (Date: 13.11.2019 Decision No: 2019/321).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article / Orijinal Araştırma

The Effect of Motivational Interview on the Treatment Adherence of the Depression Patients

Depresyon Hastalarına Yapılan Motivasyonel Görüşmenin Tedavi Uyumuna Etkisi

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Abstract

Aim: Depression is one of the most common psychiatric disorders, and treatment non-adherence is one of the important problems that negatively affect treatment outcomes in the treatment of depression. The aim of this study is to determine the effect of motivational interview on the treatment adherence.

Material and Method: This study is a control group experimental research with pre-test and post-test repetitive measurements. The sampling of the study consists of 81 depressive patients, 40 experimental and 41 controls, who applied to the Psychiatry service/polyclinic of the Training and Research Hospital. The personal information form and The Morisky Medication Adherence Scale (MMAS) were used in data collection.

Results: As a result of the motivational interviews, the MMAS scores of the experimental group decreased to a significant level in the mid-test and post-test compared to the pre-test, and no significant difference was found in the mean scale scores of the control group without intervention (p>0.05).

Conclusion: It has been found that motivational interviews are an effective intervention to improve medication adherence in the patients with depression. Healthcare professionals can facilitate adherence with the medical treatment regimen in depressed patients through motivational interview practices.

Keywords: Depression, treatment adherence, motivational interview

Öz

Amaç: Majör depresyon en sık görülen psikiyatrik bozukluklardan biridir. Tedavi uyumsuzluğu depresyon tedavisini olumsuz etkileyen önemli bir sorundur. Bu çalışmanın amacı motivasyonel görüşmenin tedaviye uyum üzerindeki etkisini belirlemektir.

Gereç ve Yöntem: Bu çalışma, ön test ve son test tekrarlı ölçümlerin yapıldığı kontrol gruplu deneysel bir araştırmadır. Araştırmanın örneklemini bir Eğitim ve Araştırma Hastanesi Psikiyatri servis/polikliniğine başvuran 40 deney ve 41 kontrol olmak üzere 81 depresif hasta oluşturmaktadır. Veri toplamada kişisel bilgi formu ve Morisky İlaç Uyum Ölçeği (MMAS) kullanılmıştır.

Bulgular: Motivasyonel görüşmeler sonucunda deney grubunun MMAS puanlarının ara test ve son testte, ön teste göre anlamlı düzeyde düştüğü, müdahale yapılmayan kontrol grubunun ölçek puan ortalamalarında ise anlamlı bir fark bulunmadığı saptanmıştır (p>0,05).

Sonuç: Motivasyonel görüşmelerin depresyon hastalarında ilaç uyumunu artırmada etkili bir müdahale olduğu saptanmıştır. Sağlık profesyonelleri, motive edici görüşme uygulamaları ile depresif hastalarda tıbbi tedavi rejimine uyumu kolaylaştırabilir.

Anahtar Kelimeler: Depresyon, tedavi uyumu, motivasyonel görüşme

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INTRODUCTION

Treatment adherence requires regular visits, completing the treatment program, regular use of medications and following the recommended behavioral changes.[1] Although patients with depression pose a significant public health burden and have effective treatments, most patients do not receive adequate treatment, and non-adherence with the treatment regimen is observed due to skipping doses and early discontinuation of the treatment.[1,2] The treatment non-adherence is an important problem in the mental disorders. It is of great importance for healthcare professionals to know the attempts that can be taken to prevent treatment non-adherence that causes recurrent hospitalizations of the patients with mental disorders and negatively affects their quality of life.

The studies on the treatment non-adherence in psychiatric disorders have increased in the recent years. However, studies on what can be done to prevent the treatment non-adherence and solutions for it are very limited. For this reason, the World Health Organization (2003) recommends developing strategies that increase the treatment adherence.[3] To our knowledge, this is the first attempt to determine factors associated with treatment adherence under the WHO multidimensionally in chronic illness in primary care settings in Spain. This report that notifies "in developed countries, adherence among patients suffering chronic diseases averages only 50%".[3] Motivational interview is used to resolve the dilemma and help the person steer towards change. It has been observed that applying motivational interview even for a session before the discharge increases depressive outpatients' treatment adherence.[4]

Symptoms associated with depression (such as lack of motivation, low energy and fatigue, decreased problem-solving ability, decreased concentration, low self-esteem) pose challenges for initiating treatment and optimal participation in the therapeutic process. Also the increasing prevalence of depression in the population has increased the need for the treatment of depression and the development of treatment interventions. Empowering the patients in managing the illness during their stay in the clinic, and ensuring the medication adherence should be among the primary goals of healthcare professionals. In non-adherence with the treatment, the psychiatric nurses can facilitate the adherence to the medical treatment regimen thanks to the therapeutic relationship and the effective communication.

There are evidences that motivational interview is effective in increasing the medication adherence in psychiatric and chronic diseases.[5-7] However, studies evaluating the effect of motivational interviewing on depression have not been found in the national literature. The aim of this study is to evaluate the effect of motivational interview on the treatment adherence.

MATERIAL AND METHOD

The population of the experimental study consists of depressed patients who applied to a Training and Research Hospital Psychiatry service/outpatient clinics between 01.09.2019-01.03.2020. The sample size (G Power: confidence interval α=0.05, power of the test (1-β) 0.95, effect size dz=1.5169455) was calculated as a total of 26 patients, 13 patients in the experimental group and 13 patients in the control group.[8] The study was started with 87 patients (44 patients for the experiment group, 43 patients for the control group), 4 patients were excluded because they did not attend the regular controls, 1 patient was excluded because of city change, and 1 patient was also excluded because he did not participate in the mid-test. The current study was completed with 81 patients, including 40 patients for the experimental group and 41 patients for the control group. The randomization method was used to determine the patients in the experimental and control groups.

The criterias for volunteers to be included in the research can be listed as; being diagnosed with depression, taking medication for at least one month, answering "yes" to at least one item of the Morisky Medication Adherence Scale, being 18 years of age or older, being literate, speaking Turkish, being able to understand the study and give the informed consent. The patients with mental retardation at a level that could not communicate meaningfully, with hearing or speech disorders, who did not have enough education to evaluate the scale, and who had any diagnosis of depression, dementia and other cognitive disorders with psychotic features according to DSM V were excluded from the study.

Data Collection Tools

The Personal Information Form: The personal information form consists of questions about the socio-demographic characteristics of the patients participating in the study, information about their diseases, and the drugs they used.

The Morisky Medication Adherence Scale (MMAS): It was developed by Donald E. Morisky, and its validity study was conducted by Morisky, Gren and Levine in 1986.(9) The Turkish validity and reliability of the scale was made by Bahar in 2013.(8) The scale consists of four questions that measure treatment adherence and filled by the patients themselves. The questions can be answered as "yes/no". If the answers are "no" to all of the questions, the adherence is considered high, if one or two questions are answered "yes", the adherence is considered medium, and if three or four questions are answered "yes", the adherence is considered low. In Bahar's (2013)(8) study, the Cronbach alpha reliability coefficient was determined as 0.62. In this study, the Cronbach alpha reliability coefficient was found to be 0.65.

Data Analysis

IBM SPSS Statistics 22.0 (IBM Corp. Armong, New York, AB) program was used for data analysis. A value of $p<0.05$ was considered statistically significant. The descriptive analyzes

(percentage, arithmetic average, etc.) were used for the data obtained from the Personal Information Form. The Shapiro-Wilk test was used to test whether the data conformed to the normal distribution, the mean and standard deviation for the MMAS mean score, and the t-test/Mann Whitney U Test in independent groups to compare the mean scores of the experimental and control groups.

Ethical Statement

Ethics committee approval (Date: 17.07.2019, Decision no: 2019/255) were obtained in order to conduct the study. Before the data were collected, the participants were informed about the research and their written consents were obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Process

The patients constituting the sample of the study were directed to the researcher by the psychiatrist. In the first interview, individuals who were admitted to the psychiatry polyclinic or hospitalized in psychiatry services, and who met the research criteria were informed about the purpose and process of the study, and those who wanted to participate and continue the study signed the Informed Consent Form, and then the Personal Information Form and the MMAS were applied. In the first meeting, the motivational interview was made individually, the contact information of the patients was obtained and the date of the next interview was determined. All interviews were conducted face to face by the researcher, who received motivational interview training. The interviews were made in the interview room in the clinical section of the specified hospital.

Throughout the study, the experimental and control group patients continued to receive their routine treatment. A total of 6 motivational interviews were conducted with the patients in the experimental group, once a week throughout the six weeks, on the specified days. The patient was followed up by completing the MMAS at the first encounter, at the 6th week and at the 3rd month. During this time period, no intervention other than the routine treatments was applied to the control group.

Content of the Motivational Interview Process

It has been reported in the literature that more than half of the patients treated with a diagnosis of depression discontinued the treatment within three weeks (Demirkol & Tamam, 2016). Motivational interviews were determined as six weeks to ensure continuity in drug use. A program consisting of six interviews, in which motivational interviewing principles were used, was applied to increase adherence to treatment in individuals with a diagnosis of depression in the experimental group. In the first interview, patients' views on the disease and the treatment they used were evaluated. The second interview focused on understanding the symptoms of the disease, evaluating the benefits and side effects of the treatment, and identifying the factors that prevent regular drug use. In the third interview, the topics in the previous interview were reviewed, drug compliance problems were determined and the patients' thoughts on non-acceptance were focused on. In the fourth interview, ambivalent emotions were evaluated and it was aimed to encourage change. In the fifth interview, the aim is to support the development of adherence. The last interview focused on the willingness of the patients to continue their treatment and the continuation of compliance.

RESULTS

When the socio-demographic characteristics of the patients included in the study were examined (**Table 1**), it was seen that the majority of the patients (67.9%) were female. 32.1% of the patients were between the ages of 48-65, and the majority (42%) had primary school education. 66.7% of the patients were married and 55.6% of them had a medium income. All variables except gender were similar between the experimental and control groups (p>0.05).

Table 1: The Comparison of Experimental and Control Groups' Patients by Socio-demographic Characteristics

Characteristics		Groups				Total		Test and p Values
		Control		Experimental				
		n	%	n	%	n	%	
Gender	Female	33	80.5	22	55.0	55	67.9	X2=6.035
	Male	8	19.5	18	45.0	26	32.1	p=0.014
Age	18-27	6	14.6	9	22.5	15	18.5	X2=3.469 p=0.325
	28-37	9	22.0	13	32.5	22	27.2	
	38-47	12	29.3	6	15.0	18	22.2	
	48-65	14	34.1	12	30.0	26	32.1	
Educational Status	Literate	5	12.2	1	2.5	6	7.4	X2=5.714 p=0.126
	Primary School	20	48.8	14	35.0	34	42.0	
	Middle School	6	14.6	10	25.0	16	19.8	
	High School andAbove	10	24.4	15	37.5	25	30.9	
Marital Status	Married	29	70.7	25	62.5	54	66.7	X2=0.617 p=0.432
	Single/Widow	12	29.3	15	37.5	27	33.3	
Income Level	Equal to Expenses	19	46.3	26	65.0	45	55.6	X2=4.188 p=0.123
	Less Than Expenses	15	36.6	12	30.0	27	33.3	
	More Than Expenses	7	17.1	2	5.0	9	11.1	
Total		41	100.0	40	100.0	81	100.0	

More than half of the patients (58%) have been followed up with a diagnosis of depression for more than 1 year. 74.1% of the patients stated that they did not receive information about the drugs included in their psychiatric treatments. 67.9% of the patients stated that they changed the drug dose. When the reasons for changing the drug dose are examined, it was determined that the dose increased when the complaints increased (17.3%), the occurrence of side effects (17.3%), the reduction of dose when the complaints decreased (14.8%), the thought of being able to do without medication (12.3%), and the forgetfulness (6.2%) were observed. When the discontinuation of drug treatment is examined, it was found that 93.8% of them intermittently stopped their treatment. Among the reasons for the discontinuation of drug treatment, it was determined that the thought that I would do without medication (24.7%), the thought that the treatment did not work (18.5%), the forgetfulness (18.5%) and the fear of addiction (13.6%) were observed with high rates. There was no statistically significant difference between the experimental and control groups in terms of the illness and treatment characteristics, and the groups were similar (p>0.05) (**Table 2**).

In the post-test, it was determined that the mean MMAS scores of the patients in the experimental group compared to the control group (p<0.001, **Table 3**). **Table 4** shows the in-group comparison of the pre-test, mid-test and post-test MMAS mean scores of the experimental and control groups. It was seen that the mean MMAS scores of the experimental group decreased in the pre-test (2.68±0.75), in the mid-test (1.51±0.59), and in the post-test (0.29±0.46). In the comparison of the mean MMAS scores of the experimental group within the group, it was found that there was a significant decrease in the mid-test and the post-test compared to the pre-test (p<0.001). In the control group, as a result of the analysis, there was no significant difference in the mid-test and post-test compared to the pre-test (p>0.05).

Table 3: The Comparison of Experimental and Control Groups' Pre-test, Mid-test and Post-test Morisky's Questions-Self-Report Measure of Adherence Mean Scores between the Groups

		MMAS			
	Groups	**n**	**X ±SD**	**Test Value**	**Significance**
Pre-test	Experimental	41	2.68±0.75	t=-1.957	p=.054
	Control	40	2.97±0.57		
Mid-test	Experimental	41	1.51±0.59	t=-7.321	p=.001
	Control	40	2.55±0.67		
Post-test	Experimental	41	0.29±0.46	t=-19.590	p=.001
	Control	40	2.72±0.64		

MMAS: Morisky Medication Adherence Scale

Table 4: The In-group Comparison of Experimental and Control Groups' Pre-test, Mid-test and Post-test Morisky's Questions-Self-Report Measure of Adherence Mean Scores

	n	**X±SD**	**Test Value**	**Significance**
MMAS - Experimental Group				
Pre-test	41	2.68±0.75	F=394.41	p=.001
Mid-test	41	1.51±0.59		
Post-test	41	0.29±0.46		
MMAS - Control Group				
Pre-test	40	2.97±0.57	F=3.824	p=.058
Mid-test	40	2.55±0.67		
Post-test	40	2.72±0.64		

MMAS: Morisky Medication Adherence Scale

Table 2: The Comparison of Patients in the Experiment and Control Groups According to Disorder and Treatment Characteristics

Characteristics		**Groups**				**Total**		**Test and p Values**
		Control		**Experimental**				
		n	**%**	**n**	**%**	**n**	**%**	
Duration of Disorder	3 months -1 year	19	46.3	15	37.5	34	42.0	X2=0.650
	More than 1 year	22	53.7	25	62.5	47	58.0	p=0.420
Getting Information About the Medication	Yes	10	24.4	11	27.5	21	25.9	X2=0.102
	No	31	75.6	29	72.5	60	74.1	p=0.749
Number of Medications Used	1	6	14.6	6	15.0	12	14.8	X2=1.206 p=0.752
	2	27	65.9	28	70.0	55	67.9	
	3	6	14.6	3	7.5	9	11.1	
	4 and above	2	4.9	3	7.5	5	6.2	
Changing the Medication Dose	Yes	31	75.6	24	60.0	55	67.9	X2=2.264
	No	10	24.4	16	40.0	26	32.1	p=0.132
Reasons for Changing the Medication Dose	-I did not change the dose	10	24.4	16	40.0	26	32.1	X2=4.192 p=0.522
	-The increase in dose when the complaints increased	9	22.0	5	12.5	14	17.3	
	-The Reduction in dose when the complaints reduced	5	12.2	7	17.5	12	14.8	
	-Because of side effects	9	22.0	5	12.5	14	17.3	
	-The thought of being able to do without medication	5	12.2	5	12.5	10	12.3	
	-The forget fullness	3	7.3	2	5.0	5	6.2	
Giving Up the Medication	Yes	37	90.2	39	97.5	76	93.8	X2=1.841
	No	4	9.8	1	2.5	5	6.2	p=0.175
Reasons for Giving Up the Medication	-I did not give up	4	9.8	1	2.5	5	6.2	X2=7.502 p=0.379
	-Because of side effects	5	12.2	2	5.0	7	8.6	
	-The thought that the treatment did not work	9	22.0	6	15.0	15	18.5	
	-The thought of I would do without medication	9	22.0	11	27.5	20	24.7	
	-Because of Forgetfulness	5	12.2	10	25.0	15	18.5	
	-Fear of addiction	4	9.8	7	17.5	11	13.6	
	-Difficulty in medication supply	4	9.8	3	7.5	7	8.6	
	-The thought of recovery	1	2.4	0	0.0	1	1.2	
Total		41	100.0	40	100.0	81	100.0	

DISCUSSION

The treatment adherence is an important aspect of effective clinical management.[10] The treatment non-adherence may lead to deterioration in the mental health status of the individual, and the relapse of depression, as well as personal and social costs.[11,12] The most common adherence problems observed in patients with depression are skipping the doses and the early discontinuation of the treatment.[2] It has been reported in the studies that more than half of the patients treated with a diagnosis of depression discontinued the treatment within three weeks.[1,2] In one study, it was reported that more than 43% of patients did not comply with their long-term treatment.[13]

The insufficient knowledge about the treatment is among the factors related to non-adherence to the treatment in psychiatric illnesses. In the current study, 74.1% of the patients stated that they did not receive information about the drugs included in their psychiatric treatments. 67.9% of the patients reported that they changed the drug dose, 93.8% of them intermittently stopped their treatment. These findings suggest that the levels of treatment non-adherence may be related to the lack of information. Informing the patients is of great importance in preventing the dose changes and the withdrawal behaviors of the medication.

In one study, the majority of patients did not continue drug treatment; It has been reported that they discontinued the drug due to side effects, did not believe in the treatment, and thought that they did not benefit from the medical treatment.[14] In our study, when the reasons for changing the medication dose and the discontinuation of the medication were examined, it was found that the behaviors of believing that they could succeed without the drugs, thinking that the treatment was not working, being affected by side effects, the fear of addiction, and the forgetfulness were common. Due to the fact that depression requires long-term treatment, patients may think that they cannot improve or the treatment is not effective, and they may disrupt their medication adherence.

In our study, the forgetfulness was noted in the reasons why the patients gave up the treatment and changed the medication dose. In the study of Burra et al.[15] the practical problems (such as forgetting or a change in routine) were identified as the most frequently defined reasons for non-adherence. In the same study, it was found that the patients gave up the medication because they thought that the antidepressants were addictive. It was observed that our study findings were consistent with the literature.

Due to the fact that motivational interviews are designed to help patients resolve the indecision for change, this approach seems appropriate for improving the medication adherence.[16] Considering that the patients are faced with many ambivalent variables such as the treatment motivation, side effects, stigmatization, and poor treatment response, motivational interview may contribute to the treatment adherence. "Motivational pharmacotherapy", in which the antidepressant treatment is combined with the motivational interviews, is a counseling approach that can be used in all health conditions, even during the short medical visits, and it is also seen as an effective practice in increasing the treatment adherence.[17,18] Before the motivational interviews, it was determined that the treatment adherence levels of the patients in both the experimental and control groups were "low". Immediately after the motivational interview application, it was observed that the medication adherence of the depressive patients in the experimental group was moderate, and at the end of the 3-month follow-up, their medication adherence was high. However, there was no significant change in the patients in the control group over time, and it was determined that their treatment adherence was still low. In our study, it was found that motivational interviews are effective in improving the medication adherence.

In one study, it was reported that motivational interview is a promising intervention that can be applied in the clinical practice to improve the medication adherence among the adult patients with depression.[19] Zygmunt et al.[20] emphasized that the motivational interview technique is more effective than psycho education in increasing the psychotic patients' treatment adherence. In a meta-analysis study by Hettema et al.[17] it was determined that the motivational interviews increased the treatment adherence. It has been reported in the literature that the motivational interviews are effective in facilitating the illness management and can provide significant benefits for the psychiatric support services in the community.[21] The studies support the value of adding the motivational interviews to existing treatments in order to enhance the treatment adherence and improve the clinical outcomes. Our study results confirm this explanation.

Limitations

The most important limitation of the current study is that it is a mono-center and cross-sectional study. Planning studies that are multi-centered, with a wider sample group, and exclude cultural factors can provide more advanced results.

CONCLUSION

In this study, it has been observed that the practice of motivational interviews is effective in improving the medication adherence of the patients with depression. In line with the results obtained, it has been shown that the motivational interviews can be a solution to eliminate the non-adherence in depression treatment, and can support the recovery in depression by improving the adherence. It can be recommended that healthcare professionals improve their skills by receiving motivational interviewing training and standardize the application of motivational interviewing in patients with treatment non-compliance.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziantep Universty Ethic Committee. (Date: 17/07/2019 Decision No: 2019/255).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article / Orijinal Araştırma

Investigation of Venous Thromboembolism Prophylaxis Practices in Spinal Fusion Surgery and Outcomes: A Single Center Experience

Spinal Füzyon Cerrahisinde Venöz Tromboemboli Profilaksisi Uygulamalarının ve Sonuçlarının İncelenmesi: Tek Merkez Deneyimi

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Abstract

Aim: Venous thromboembolism (VTE) is among the most common causes of preventable hospital-acquired deaths. VTE is known as deep vein thrombosis (DVT) when it occurs in the veins and pulmonary embolism (PE) when it occurs in the lungs and is common in surgery practice. We aimed to determine the frequency of venous thromboembolism (VTE), the factors affecting the development of VTE, and the types and effectiveness of VTE prophylaxis applications in patients who underwent spinal fusion surgery (SFS).

Material and Methods: The patients aged over 18 who underwent SFS for spinal fracture or thoracolumbar stenosis in our neurosurgery clinic between June, 2020 and December, 2022 were included. The patients records were evaluated retrospectively. VTE prophylaxis was given according to the Caprini risk score.

Results: A total of 137 patients, 85 (62%) of female, with a meanage of 48.6±+8.77 years were included in the study. According to the Caprini risk scores, 90 (65.7%) of the cases were at high risk. VTE was detected in four patients (2.9%) despite prophylaxis (3 cases of DVT and one pulmonary embolism).

Conclusion: Although VTE prophylaxis is performed according to Caprini risk score in SFS, it is seen that embolisms cannot be prevented sufficiently. Therefore, studies with a high level of evidence are needed for the use of these algorithms in SFS.

Keywords: Caprini score, prophylaxis, spinal fusion surgery, venous thromboembolism

Öz

Amaç: Venöz tromboembolizm (VTE), önlenebilir hastane kaynaklı ölümlerin en yaygın nedenlerinden biridir. VTE, damarlarda meydana geldiğinde derin ven trombozu (DVT), akciğerlerde meydana geldiğinde pulmoner emboli (PE) olarak bilinir ve cerrahi pratikte sık görülür. Spinal füzyon cerrahisi (SFS) uygulanan hastalarda VTE sıklığını, gelişimini etkileyen faktörleri ve profilaksisi uygulamalarının türlerini ve etkinliğini belirlemeyi amaçladık.

Gereç ve Yöntem: Nöroşirürji kliniğimizde Haziran 2020 ile Aralık 2022 tarihleri arasında omurga kırığı veya torakolomber darlık nedeniyle SFS uygulanan 18 yaş üstü hastalar dahil edildi. Hasta kayıtları retrospektif olarak değerlendirildi. Caprini risk skoruna göre VTE profilaksisi verildi.

Bulgular: Çalışmaya ortalama yaşları 48.6±+8.77 olan 85'i (%62) kadın olmak üzere toplam 137 hasta dahil edildi. Caprini risk skorlarına göre olguların 90'ı (%65,7) yüksek riskli idi. Profilaksiye (3 DVT ve 1 pulmoner emboli) rağmen dört hastada (%2,9) VTE saptandı

Sonuç: SFS'de VTE profilaksisi Caprini risk skoruna göre yapılmasına rağmen embolilerin yeterince önlenemediği görülmektedir. Bu nedenle bu algoritmaların SFS'de kullanımı için kanıt düzeyi yüksek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Caprini skoru, profilaksi, spinal füzyon cerrahisi, venöz tromboembolizm

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INTRODUCTION

Venous thromboembolism (VTE) is among the most common causes of preventable hospital-acquired deaths.[1] VTE is known as deep vein thrombosis (DVT) when it occurs in the veins and pulmonary embolism (PE) when it occurs in the lungs and is common in surgery practice. Increased risk of VTE due to prothrombotic conditions triggered during surgery, perioperative venous stasis and immobility of patients in the postoperative period. In addition, delayed mobilization of patients due to postoperative pain and neurological problems in spinal fusion surgery (SFS) also increases the risk of VTE.[2] Upto 600,000 hospital admissions for DVT and PE and a mortality rate of upto 50,000 occur annually in the United States of America (USA), with a significant portion of these coming from orthopedic surgical procedures.[3]

VTE thromboprophylaxis in SFS is still controversial. In the last decade, several studies have analyzed VTE prophylaxis, but there is no consensus on the timing and effective use of these interventions.[4] The estimated incidence of VTE after spine surgery varies between 0.2-31% according to different studies.[5] This rate has been reported to be 50-100% in traumatic spinal cord injury patients.[6] There are two main categories of risk variables that raise incidence of VTE: patient-related risk factors and surgery-type-related risk factors. Among the factors related to patients, the presence of multiple trauma, active cancer disease, and spinal cord injury are considered high risk.[7] Many other risk factors such as age, hypertension, diabetes mellitus, hyperlipidemia, heart failure, and body mass index may also be effective.[8] Therefore, certain classifications have been made and put into practice to determine the risk of VTE and to apply prophylaxis.[9] There are mechanical and pharmacologic applications in VTE prophylaxis in spinal fusion surgeries. However, bleeding may ocur during or after surgery in pharmacologic VTE prophylaxis applications. Therefore, the decision for VTE prophylaxis is of great importance.[10] Despite the existence of several efficient mechanical and pharmacological thromboprophylaxis therapies, it is stil unclear how these procedures fit into SFS. To balance, the danger of mortality from a thromboembolic consequence, spine surgeons must make a tough choice.[11] However, less is known about ideal applications of chemoprophylaxis for SFS. Due to the relative paucity of good quality evidence on the efficacy and safety of VTE prophylaxis in SFS, surgeons' clinical practice varies widely and is often based on surgeons' experience.[10]

In this study, we sought to reveal the frequency of VTE, the factors affecting the development of VTE and effectiveness of VTE prophylaxis applications in patients who underwent SFS.

MATERIAL AND METHOD

Patient Selection

This study was carried out in compliance with the principles of the Declaration of Helsinki upon the approval dated April 01, 2023 and numbered 2023/01-19 of the Clinical Research Board of Ethics of the Faculty of Medicine. In the present study, the patients aged over 18 who underwent SFS for spinal fracture or thoracolumbar stenosis in our neurosurgery clinic between June, 2020 and December, 2022 were included. The patient's records were evaluated retrospectively.

Exclusion Criteria

Patients with a previous history of VTE and patients under the age of 18 were excluded from the study. In addition, patients with cervical fractures or cervical stenosis who underwent SFS were excluded from the study.

Surgical Method and VTE Prophylaxis

SFS is considered a major surgical procedure. All SFS patients were operated on in the prone position. Patients were divided into short-segment SFS (two levels) or long-segment SFS (≥3 levels).

Compression stockings or elasticbandages were applied to all patients for VTE prophylaxis in the perioperative period. All operated patients were mobilized on the first day of the post operative period (early postoperative period). According to Caprini scoring, LMWH was given to high-risk patients. We did not give LMWH if they were not high-risk and did not have other underlying diseases.

Caprini Risk Assessment Model

The Caprini Risk Assessment Model (RAM) was initially developed for both surgical and medical patients. Despite the fact that there is strong evidence to support its validity in surgical patients.[11] More than 100 clinical trials conducted world wide involving more than 250 000 patients validated the Caprini RAM. The correct completion of the Caprini RAM determines the best course of treatment in the end. In every patient group where it has been fully evaluated, the VTE rate climbs exponentially as the numerical score rises.[12,13] To ensure uniformity and accuracy of scoring, completion guidelines were developed as a result of this procedure. The 2013 Caprini RAM offers a reliable, comprehensive, and effective method for VTE prophylaxis selection and risk stratification.[12]

Data collection

Clinical data and radiological examinations of patients hospitalized in the Department of Neurosurgery who underwent SFS for a spinal fracture, spinal stenosis, or spondylolistesis were retrospectively analyzed. Age, gender, clinical and neurologic status at the time of admission, comorbidities, cause of surgery, type of surgery, duration of surgery, type of VTE prophylaxis, additional risk factors Hypertension (HT), diabetes mellitus (DM), coronary arterial disease (CAD), cerebrovascular disease (CVD), history of antiaggregant drugs, body mass index, platelet level, albumin level and types of medical treatments of VTE were recorded from the hospital information recording system. In addition, the effectiveness of VTE prophylaxis were investigated.

Statistical Method

The IBM SPSS 23 Windows package program was used to analyse this study's data. Demographic and proportional distributions of the subjects included in the study population were calculated as percentages. After using Kolmogorov-Smirnov to determine whether the data were normally distributed, non-parametric analysis techniques were utilized to do the analysis. Mann Whitney U Test was used for comparative statistics of the groups with each other (such as analyzing the length of hospital stay according to gender). The Cross Tabulation Chi-square test was used to reveal the relationships between the groups. "Spearman" test was used in the correlation analysis of the continuous variables in the groups. In the application of correlation tests, each group was separated with a split file and analyzed. Cross Tabulation Chi-square test was used to reveal the relationship between risk factors and Caprini risk groups. In the comparative statistical analysis of hospital stay and surgery duration by gender, the Mann Whitney U test was implemented. Correlation analysis was performed between split file and continuous variables. In the interpretation of statistical results, $p<.05$ values were accepted as significant.

RESULTS

A total of 137 patients, 85 (62%) of female, with a mean age of 48.6±8.77 years were included in the study. VTE was detected in four patients (2.9%) despite prophylaxis. **Table 1** summarizes the characteristics of the patients and the frequency of VTE. The BMI of 69 patients (50.4%) was between 31-35 (**Table 2**).

Table 1. Demographic characteristics of the cases

	N	%
Gender		
Female	85	62.0
Male	52	38.0
Surgery indication		
Vertebral fracture	28	20.4
Spondylosis	109	79.6
Type of surgery**		
Short-segment SFS	23	16.8
Long-segment SFS	114	83.2
VTE subtype		
None	133	97.1
DVT	3	2.2
PE	1	0.7

*DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: Venous thromboembolism, ** Short-segment SFS (two levels) or long-segment SFS (≥3 levels).

Table 2. Distribution of patients according to BMI groups

BMI	N	%
20-25	6	4.4
26-30	30	21.9
31-35	69	50.4
36-40	30	21.9
41 and over	2	1.5

*BMI: body mass index

Hypertension was the most common co-morbidity and it was detected in 51 (37.2%) cases (**Table 3**).

Table 3. Distribution of patients according to underlying co-morbidities

Co-morbidities	N	%
None	43	31.4
HT	51	37.2
DM	16	11.7
CVD	4	2.9
CAD	15	10.9
Antiaggregant use	8	5.8

*CAD: coronary arterial disease, CVD: cerebrovascular disease, HT: hypertension, DM: diabetes mellitus.

According to the Caprini scores, 90 (65.7%) of the cases were at high risk (**Table 4**).

Table 4. Distribution of cases according to Caprini score

Caprini Score	n	%
Very low risk	0	0
Low risk	4	2.9
Moderate risk	43	31.4
High risk	90	65.7

Depending on the type of operation, the included patients were divided into different groups. In long-segment patients, the duration of operation increased, hospital stay increased and albumin levels decreased. In patients who underwent long-segment surgery, the duration of hospital stay increased when the operation time increased ($p<0.01$), and the albumin levels of these patients were also lower $p<0.05$. In patients who underwent short-segment surgery, there was no statistical significance between the duration of hospital stay and albumin levels. There was no significant correlation between Caprini low risk group and operation time, albumin level, platelet count, and length of hospital stay.

In the Caprini medium-risk group, there was a significant correlation in the direction of an increase in the length of hospital stay only as the operation time increased ($p<0.01$). In the Caprini high-risk group, it was observed that the operation time increased with age ($p<0.05$).

Hospital stay and operation times were compared according to gender. It was observed that male (6.9±3.6 days) had a significantly shorter hospital stay than female (8.4±3.2 days) ($p<0.01$). On the other hand, female (3.8±1.2 hours) had a shorter operation times than male (4.0±1.5 hours), but this difference was not statistically significant ($p>0.05$).

According to Kruskal-Wallis test results, there was no significant relationship between the presence of additional risk factors and the development of VTE ($p>0.05$). In addition, there was no significant relationship between additional risk factors and albumin and thrombocyte levels ($p>0.05$). Among subjects without risk factors, the proportion of those with moderate Caprini risk level (n=25, 58%) was significantly higher than those with high Caprini level (n=14, 32.6%) ($p<0.001$).

When the Caprini scores of hypertensive patients were analyzed, the number of patients with high Caprini scores (n=40, 78.4%) was significantly higher than those with moderate risk (n=11, 21.6%) ($p<0.001$). All of those with CAD (n=15, 100%) and a history of antiaggregant use (n=8 ,100%) were in the high-risk group according to the Caprini score ($p<0.001$). Patients with CVD and diabetes mellitus as risk factors had similar Caprini scores, with no noticeable statistically difference ($p>0.05$).

There was no significant relationship between the BMI categories of the subjects with HT, CVD, CAD, or antiaggregant use. However, when the BMI categories of 16 DM cases were compared, BMI=31-35 (n=6, 37.5%) and BMI=36-40 (n=7, 43.8%) were clustered and there was a significant difference between them and the others ($p<0.05$).

DISCUSSION

Statement Of Principal Findings

In our patients included in this study who underwent SFS, we found 4 (3 DVT, 1 PE) VTE in 2.9%, although thromboembolism prophylaxis was performed according to the Caprini score. These VTE incidence results we obtained are relatively lower than the literature. Prophylaxis in SFS operations, even if it is done according to the Caprini score, can reduce VTE even if it does not completely prevent it, so it also helps to reduce morbidity rates.

Interpretation within the Context of the Wider Literature

According to the findings of previous studies, surgical patients appear to be at a higher risk than medical patients for VTE, with over half of all hospitalized patients globally at risk. Moreover, only 50% of at-risk patients got a prophylactic treatment suggested by the American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients.[14] Prior research revealed that rates of total VTE prevention ranged from 13% to 64%.[14-16] Given the varied character of the scant studies that have been published in the literature, it is challenging to estimate the true incidence eventhough DVT and PE are quite uncommon regardless of the kind of prophylaxis. Given the relatively high probability of fatal PE, a new meta-analysis hypothesizes that chemoprophylaxis may be involved.[17] In the USA, PE, DVT, and VTE are the most common avoidable causes of cardiovascular disease and the main cause of preventable mortality after surgery. Many immediate and long-term problems are connected to postoperative VTE.[18] For all these reasons we have planned this study. In our study, we aimed to retrospectively evaluate our VTE prophylaxis practices in SFS, which is considered major surgery and to reveal the characteristics of patients who developed VTE despite these practices. In this study including 137 patients who underwent SFS, VTE was detected in four (3 DVT,1 PE) patients. Mortality did not develop in any patient.

The American Society of Hematology 2019 guideline offered conditional recommendations against inferior vena cava filters, no prophylaxis for mechanical prophylaxis, and graded compression stockings for pneumatic compression prophylaxis for patients undergoing major surgery. Conditional recommendations for patients undergoing total hip or total knee arthroplasty included the use of acetylsalicylic acid or anticoagulants, direct oral anticoagulants rather than LMWH. Using LMWH or unfractionated heparin, the recommendation advocated pharmacologic prophylaxis for major general surgery over no prophylaxis. The use of pharmaceutical prophylaxis prior to major neurosurgery, transurethral prostate resection, or radical prostatectomy is discouraged by this guideline. According to this recommendation, pharmacologic prophylaxis was preferable to no prophylaxis for major gynecologic or trauma surgeries.[14] Patients included in the present study received VTE prophylaxis according to the Caprini RAM. A total of 90 patients (65.7 %) were in the high risk group according to Caprini score. For VTE prophylaxis, LMWH (Nadroparin, is an anticoagulant belonging to a class of drugs called LMWH) was preferred. Compression stockings or elastic bandages were applied to all patients for VTE prophylaxis in the peri-operative period. All operated patients were mobilized on the first day of the postoperative period. Although an increase in the length of hospital stay and a decrease in albumin levels were observed in our long-segment SFS patients, there was no significant relationship between the length of hospital stay and albumin levels in short-segment SFS patients.

In a meta-analysis study conducted by Chao Zhu et al. in 2020 on spinal surgery, it was reported that the prolongation of the operation time was effective in the decrease in hemoglobin and albumin levels and the development of postoperative delirium.[19]

According to a meta-analysis published in 2021 that included a total of 8373 patients, there was a significant difference between groups in the incidence of postoperative DVT, but not in the incidence of VTE. Both groups had a low incidence of serious bleeding episodes and spinal epidural hematomas.[20] The general strategy for non-orthopedic surgery continues to be the evaluation of the thrombosis risk with the advice to utilize a risk assessment instrument like the modified Caprini score. In non-orthopedic surgery, LMWH seems to be more effective for VTE prevention than unfractionated heparin. Recent trials have shown acetylsalicylic acid as a viable choice for VTE prevention following total hip, total knee, and hip fracture surgery in orthopedics. Prolonged prophylaxis with LMWH lowers the risk of symptomatic VTE in high-risk abdominal and pelvic cancer surgeries without noticeably raising the risk of bleeding, and it lowers the risk of symptomatic VTE in major orthopedic surgeries but results in more mild but manageable bleeding.[21] In our study, severe bleeding episodes and spinal epidural hematoma were not detected in any patient receiving LMWH for VTE prophylaxis.

A similar study[21] involving 107 patients found that despite having a high risk of VTE, patients under going elective instrumental posterior lumbar spinal fusion actually have a very low incidence of VTE. In order to prevent VTE complications in these patients, this study's data support use of mechanical prophylaxis with thromboembolic prevention stockings and calf compression devices.[22] Another similar study examined 2366 elective spinal procedures in 2181 adults over all. All patients were provided with anti-embolic stockings, early mobilization, and properhydration. Additionally, 29% of patients (689) received LMWH while they were hospitalized. A peri-operative protocol that includes anti-embolic stockings, hydration, and early postoperative mobilization has been shown to significantly lower the incidence of VTE, and the addition of LMWH is safe in patients who are at high risk of developing VTE.[23] In our study, all patients received mechanical thromboprophylaxis. However, differently, we also applied medical prophylaxis according to the Caprini score. Despite all these, the rate of VTE developed, albeit at a low rate.

The variety in the way that the Caprini RAM is implemented between centers limits its effectiveness. In terms of the number of risk categories employed, the cut points used to define the risk categories, the result being monitored, and the follow-up period, the score-derived VTE risk classification exhibits substantial variety. This influences the clinical and scientific implications of the findings since it causes equivalent risk groups to be linked with differing VTE rates. There is a need for studies that verify the Caprini RAM in a large population of medical and surgical patients, designate standard risk categories, define risk of DVT and PE as different end objectives, and assess outcomes at defined follow-up time periods in order to improve generalize ability.[24, 25]

However, a more effective score other than this score has not been defined in the current literature. Therefore, we examined the relationship between this score and other factors that may be effective in the development of VTE such as underlying diseases, BMI, albumin level, surgical method, length of hospital stay, and gender according to the Caprini score. In the Caprini risk classification, there was no significant correlation between low risk and operation time, albumin level, platelet count, and length of hospital stay. However, our cases with BMIs between 31 and 40 had high Caprini scores, and this elevation also leads to an increase in the risk of VTE. It is known that high BMI is one of the factors that increase the risk of VTE, and our result was compatible with the literature.[26,27] However, there was no significant relationship between the patients' BMI categories and the use of HT, CVD, CAD and antiaggregant use.

Implications For Policy, Practice And Research

In the Caprini medium-risk group, there was a significant correlation in the direction of an increase in the length of hospital stay only as the operation time increased. In the Caprini high-risk group, the duration of surgery was observed to increase significantly with age. It is seen that Caprini scores of patients with history of antiaggregant use and hypertension are higher.

Limitations and Advantages

This retrospective study was a single-center study and one of the most prominent limitations of the study is the small sample size. However, the fact that there is no similar study published in our country is the superiority of the study. Therefore, prospective observational studies are needed.

CONCLUSION

In conclusion, early postoperative patient mobilization and using mechanical anti-embolic stockings are effective in lowering the incidence of VTE. For the vast majority of patients having elective spinal surgery, this protocol seems to be safe. However, it is safe to administer LMWH while a patient is hospitalized if they have risk for VTE. The VTE risk can be calculated using the Caprini RAM. Despite all precautions, VTE can not entirely be avoided. Therefore, prospective observational studies of large series are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Çanakkale Onsekiz Mart University Clinical Researches Ethics Committee (Date: 04.01.2023, Decision No: 2023/01-19).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article / Orijinal Araştırma

The Relationship between Preoperative CA 19-9 and CEA Levels and Histopathology of Tumors in Colorectal Cancer

Kolorektal Kanser Nedeniyle Opere olan Hastalarda Ameliyat Öncesi CA 19-9 ve CEA Düzeyleri ile Tümörün Histopatolojisi Arasındaki İlişki

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Abstract

Aim: Colorectal cancer (CRC) is a common and lethal disease. Since early diagnosis greatly increases the success rate of cancer treatment, the need to investigate cancer determinants in a multifaceted manner is ongoing. The tumor (T), node (N), and metastasis (M) classification of tumors is the most important prognostic indicator in colorectal cancers. In our study, the relationship between preoperative CEA and CA 19-9 values in patients with colorectal cancer and the TNM stage of cancer and its prognostic histopathological features, such as the depth of invasion of the tumor and lymphovascular and perineural invasion, was investigated.

Material and Method: A total of 153 patients diagnosed with colorectal cancer were included in the study. The histopathological data in the resection materials of the patients who were operated on by the General Surgery Department were collected from the pathology reports. Clinical data were collected through the retrospective scanning of patient files. Cases with a CEA value of 5 ng/ml and above and cases with a CA 19-9 value of 35 U/ml and above were considered positive.

Results: The median age of the patients was 64, and 51.6% of the patients were male and 48.4% female. CEA was found to be positive in 35.3% of the patients, while this rate was 20.9% for CA 19-9. In our study, CEA and CA 19-9 positivity were significantly correlated with the TNM stage of the tumor, depth of invasion, lymphovascular invasion, perineural invasion, lymph node metastasis, and distant metastasis. In addition, the mean age of the CA 19-9-positive cases was significantly higher than that of the negative ones. The mean tumor size of the CEA-positive cases was significantly higher than that of the negative ones.

Conclusion: CEA and CA 19-9 are valuable both in demonstrating advanced-stage tumors and in detecting malignancy in tumors at advanced ages. Since survival decreases with stage progression, positive CEA and CA 19-9 values are associated with a worse prognosis.

Keywords: CA 19-9; carcinoembryonic antigen; colorectal neoplasm

Öz

Amaç: Kolorektal kanser yaygın ve ölümcül bir hastalıktır. Erken tanı, kanser tedavisinin başarı yüzdesini büyük oranda arttırdığından kanser belirleyicilerinin çok yönlü olarak araştırılması gereksinimi sürmektedir. Kolorektal kanserlerde tümörün Tümör (T), Lenf Nodu (N), Metastaz (M) sınıflaması en önemli prognostik göstergedir. Çalışmamızda kolorektal kanserli hastalardaki preoperatif CEA ve CA 19-9 değerleri ile kanserin TNM evresi, tümörün invazyon derinliği, lenfovasküler ve perinöral invazyon gibi prognostik histopatolojik özellikleri arasındaki ilişki araştırılmıştır.

Gereç ve Yöntem: Çalışmaya kolorektal kanser tanısı alan 153 hasta dahil edildi. Genel Cerrahi Anabilim Dalı tarafından opere edilen hastaların rezeksiyon materyallerinde yer alan histopatolojik veriler patoloji raporlarından elde edildi. Klinik veriler, hasta dosyalarının geriye dönük taranmasıyla toplandı. CEA değeri 5 ng/ml ve üzerinde olan olgular ile CA 19-9 değeri 35 U/ml ve üzerinde olan olgular pozitif kabul edildi.

Bulgular: Hastaların yaş ortancası 64 olup, %51,6'sı erkek ve %48,4'ü kadındır. Hastaların %35,3 ünde CEA pozitif olarak saptanırken bu oran CA 19-9 için %20,9'dur. Çalışmamızda CEA ve CA 19-9 pozitifliği ile tümörün TNM Evresi, invazyon derinliği, lenfovasküler invazyon, perinöral invazyon, nodal tutulum, metastaz istatistiksel olarak anlamlı düzeyde ilişkilidir. Ayrıca CA 19-9 pozitif olguların yaş ortalaması, negatif olanlara kıyasla anlamlı derecede yüksektir. CEA pozitif olguların tümör boyutu ortalaması, negatif olanlara göre anlamlı derecede yüksektir.

Sonuç: CEA ve CA 19-9, hem ileri evre tümörü göstermede hem de ileri yaşlarda saptanan tümörlerde malignite saptanmasında değerlidir. Evre ilerledikçe sağ kalım düştüğünden pozitif CEA ve CA 19-9 değerleri her ikisi birden daha kötü prognoz ile ilişkilidir.

Anahtar Kelimeler: CA 19-9; karsinoembriyonik antijen; kolorektal kanser

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INTRODUCTION

Colorectal cancer (CRC) is a serious disease that can result in death. It is the third most common cancer in Turkey. In 2020, CRC accounted for 21,191 (9%) of 233,834 cancer cases in Turkey. Moreover, it ranks second among deaths caused by cancer. CRC caused approximately 935,000 deaths in 2020, with 1.9 million newly diagnosed patients.[1] CRC can be prevented if detected in the precancerous stage and treated if diagnosed early. Early detection of cancer or adenoma development, i.e., in the asymptomatic period, using tumor markers and screening methods significantly reduces mortality and morbidity.[2,3]

Carcinomas are malignant tumors originating from epithelial tissue and are referred to as adenocarcinomas when they form a gland structure.[4] More than 95% of CRCs are of the adenocarcinoma type and are graded according to the appearance and differentiation of the glandular structures.[5] According to this distinction, there are 3 degrees of differentiation – well differentiated (Grade-I), moderately differentiated (Grade-II), and poorly differentiated (Grade-III).

CRC staging is important in determining both the prognosis and the method of treatment.[6] It is based on the depth of the tumor and whether there are lymph nodes or distant organ metastases. The Dukes classification and its modification by Astler–Coller have been replaced by the TNM staging system.[7] The processes of staging and prognosis for patients with CRCs are shown in **Figure 1**.[8]

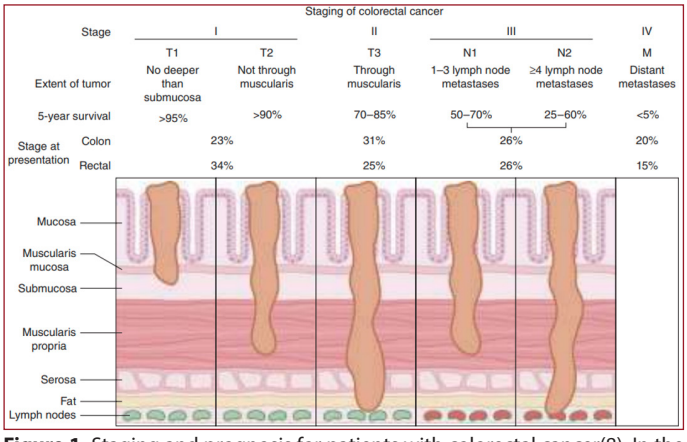

Figure 1. Staging and prognosis for patients with colorectal cancer(8). In the figure, non-metastasized lymph nodes are shown in green and metastatic lymph nodes are shown in red.

Additionally, tumor markers are substances produced by tumor tissue that can be used to distinguish a tumor from normal tissues. They can be measured by various methods to detect the presence of cancer.[9] Tumor markers, which generally represent the re-formation of substances, are produced by tissues that are embryologically closely related.[10] Markers can be used to determine the success of initial treatment (e.g., surgery, chemotherapy, or radiation) to monitor treatment, detect cancer recurrence, and determine the type of treatment. Although there have been significant advances in cancer treatment in recent years, approximately half of malignant diseases are at a stage where curative treatment is not possible when clinical symptoms appear. Therefore, tumor markers are becoming increasingly important as they help in early diagnosis.[11]

In some cases, tumor markers can provide very useful information at the diagnostic stage, in monitoring the efficacy of treatment after diagnosis, and in the post-op follow-up of patients. In our study on tumor markers, we aimed to investigate the predictive value of CEA and CA 19-9 tumor markers by comparing preoperative CEA and CA 19-9 values with histopathological prognostic features and the TNM stage of the tumor in patients operated on for colorectal cancer.

MATERIAL AND METHOD

This is a retrospective cross-sectional study in which the relationship between preoperative tumor markers CEA and CA 19-9 levels and the clinical and histopathological data of patients operated on for CRC were examined. The population of the study was 153 patients, all of whom were diagnosed with colorectal carcinoma in the Training and Research Hospital Medical Pathology Laboratory between 1 January 2014 and 1 February 2018 and operated at the General Surgery clinic. Patients over 18 years of age with post-op pathology reports and preoperative tumor markers in their files were included, and those for whom the required data were not fully met were excluded. Histopathologic data of the resection material, such as histological grade, depth of invasion, lymphovascular invasion, and perineural invasion, were obtained from the pathology reports. In addition, clinical data were collected through a retrospective review of patient files. In terms of tumor location, the colon was categorized into three groups – the right colon, the left colon, and the rectum. The cecum, ascending colon, and right half of the transverse colon were grouped into the right colon, and the left half of the transverse colon, descending colon, and sigmoid colon were grouped into the left colon. The cases with CEA values of 5 ng/ml and above and CA 19-9 values of 35 U/ml and above were considered positive. The necessary ethical approval was obtained by the Clinical Research Ethics Committee (Date: 24 January 2018 / Decision number 130).

Statistical Analysis

The IBM SPSS Statistics 22 package program was used for the statistical analyses while evaluating the findings obtained in the study. While evaluating the study data, the Shapiro–Wilk test was used to check the normal distribution. In addition, descriptive statistical methods are shown as mean, standard deviation, and frequency. A P value < 0.05 was considered significant.

RESULTS

Our study was conducted on a total of 153 patients, 74 (48.4%) females and 79 (51.6%) males. The median age was 64 (range: 39–89). The tumor was located in the rectum in 34% of

the cases, on the right side in 22.9% cases, and on the left side in 43.1% cases.

In 84.3% cases, the tumor was Grade 2, in 10.5%, Grade 1, and in 5.2%, Grade 3. While the depth of tumor invasion was T1 in only 6.5% of cases, it was T2 in 15%, T3 in 39.2%, and T4 in 39.2%. There was lymphovascular invasion in 53.6% cases and perineural invasion in 26.1% cases. Lymph node invasion was N0 in 58.8% cases, N1 in 28.1% cases, and N2 in 13.1% cases. Moreover, 9.8% cases had metastases, 35.3% cases were CEA positive, and 20.9% cases were CA 19-9 positive.

The mean ages of CEA-positive and CA 19-9-positive cases were statistically significantly higher than those of the negative cases (**Table 1**). The mean tumor size of CEA-positive cases was statistically significantly higher than that of negative cases (p: 0.022; $p < 0.05$). There was no statistically significant difference between the mean tumor sizes of positive or negative CA 19-9 cases (**Table 2**).

Table 1. Age assessment according to CEA and CA 19-9 positivity

	Age Mean±SD	p
CEA		0.033*
Positive	66.65±10.60	
Negative	62.55±11.60	
CA 19-9		0.010*
Positive	68.56±10.60	
Negative	62.79±11.33	

Student t test; Data were presented as mean±SD.; CEA: Carcinoembriogenic antigen; CA 19-9: Carbohydrate antigen 19-9; SD: Standart Deviation. CEA value of 5ng/ml and above was considered positive. CA 19-9 value of 35U/ml and above was considered positive.

Table 2. Tumor size assessment according to CEA and CA 19-9 positivity

	Tumor Size Mean±SD	p
CEA		0.022*
Positive	5.47±2.56	
Negative	4.56±2.22	
CA-19-9		0.137
Positive	5.44±2.66	
Negative	4.73±2.29	

Student t test; Data were presented as mean±SD.; CEA: Carcinoembriogenic antigen; CA 19-9: Carbohydrate antigen 19-9; SD: Standart Deviation. CEA value of 5ng/ml and above was considered positive. CA 19-9 value of 35U/ml and above was considered positive.

There was no statistically significant difference between the rates of CEA positivity according to tumor location. CEA was positive in 40.4% of rectal patients, 4.3% of right-sided patients, and 31.8% of left-sided patients. CEA positivity was observed in 37.5% Grade 1 cases, 34.1% Grade 2 cases, and 50% Grade 3 cases. There was no statistically significant difference between them. However, there was a statistically significant difference between the rates of CEA positivity according to the depth of tumor invasion (p: 0.000; $p < 0.05$). The rate of CEA positivity in T4 patients (61.7%) was significantly higher than in T1 (0%), T2 (13%), and T3 (23.3%) patients.

The rate of CEA positivity in patients with lymphovascular invasion (47.6%) was statistically significantly higher than in patients without lymphovascular invasion (21.1%) (p: 0.001; $p < 0.05$). Additionally, the rate of CEA positivity in cases with perineural invasion (52.5%) was statistically significantly higher than in cases without perineural invasion (29.2%) (p: 0.014; $p < 0.05$).

There was also a statistically significant difference between the rates of CEA positivity according to lymph node invasion (p: 0.000; $p < 0.05$). The rate of CEA positivity was 21.1% in N0 patients, 48.8% in N1 patients, and 70% in N2 patients, and it was observed that CEA positivity increased with every level.

The CEA positivity rate in patients with metastases (100%) was statistically significantly higher than that in patients without metastases (28.5%) (p: 0.000; $p < 0.05$). CEA positivity was observed in 39.2% of the women and 31.6% of the men, and there was no statistically significant difference between them (**Table 3**).

Table 3. CEA assessments by research parameters

		CEA Positive n (%)	CEA Negative n (%)	p
Tumor Location	Rectum	21 (40.4%)	31 (59.6%)	[1]0.620
	Right	12 (34.3%)	23 (65.7%)	
	Left	21 (31.8%)	45 (68.2%)	
Histological grade				[1]0.647
	Grade 1	6 (37.5%)	10 (62.5%)	
	Grade 2	44 (34.1%)	85 (65.9%)	
	Grade 3	4 (50%)	4 (50%)	
Depth of invasion				[1]0.000*
	T1	0 (0%)	10 (100%)	
	T2	3 (13%)	20 (87%)	
	T3	14 (23.3%)	46 (76.7%)	
	T4	37 (61.7%)	23 (38.3%)	
TNM stage				[1]0.000*
	Stage I	2(8%)	23(92%)	
	Stage II	14(27%)	47(73%)	
	Stage III	22(47%)	25(53%)	
	Stage IV	16(84%)	3(16%)	
Lymphovascular invasion				[2]0.001*
	Negative	15 (21.1%)	56 (78.9%)	
	Positive	39 (47.6%)	43 (52.4%)	
Perineural invasion				[2]0.014*
	Negative	33 (29.2%)	80 (70.8%)	
	Positive	21 (52.5%)	19 (47.5%)	
Lymph nodes				[1]0.000*
	N0	19 (21.1%)	71 (78.9%)	
	N1 (1-3 LN +)	21 (48.8%)	22 (51.2%)	
	N2 (4 and above +)	14 (70%)	6 (30%)	
Metastases				[2]0.000*
	Negative	39 (28.5%)	98 (71.5%)	
	Positive	15 (100%)	0 (0%)	
Gender				
	Female	29 (39.2%)	45 (60.8%)	[1]0.329
	Male	25 (31.6%)	54 (68.4%)	

1Chi-Squared Test, 2Continuity (yates) correction; T: Tumor; TNM: Tumor-LymphNode-Metastasis; CEA: Carcinoembriogenic antigen; CEA value of 5ng/ml and above was considered positive.

However, there was a statistically significant difference between the rates of CA 19-9 positivity according to tumor location (p: 0.037; p < 0.05). CA 19-9 was positive in 11.5% rectal patients, 17.1% right-sided patients, and 30.3% left-sided patients. The rate of CA 19-9 positivity was significantly higher on the left side.

CA 19-9 positivity was observed in 18.8% of Grade 1 cases, 20.2% of Grade 2 cases, and 37.5% of Grade 3 cases, and there was no statistically significant difference between them. However, there was a statistically significant difference between the rates of CA 19-9 positivity according to the depth of tumor invasion (p: 0.002; p < 0.05). The rate of CA 19-9 positivity in T4 patients (36.7%) was significantly higher than in T1 (10%), T2 (4.3%), and T3 (13.3%) patients.

The rate of CA 19-9 positivity in patients with lymphovascular invasion (32.9%) was statistically significantly higher than in patients without lymphovascular invasion (7%) (p: 0.000; p < 0.05), and the rate of CA 19-9 positivity in cases with perineural invasion (40%) was statistically significantly higher than in cases without perineural invasion (14.2%) (p: 0.001; p < 0.05).

There was also a statistically significant difference between the rates of CA 19-9 positivity according to lymph node invasion (p: 0.000; p < 0.05). The rate of CA 19-9 positivity was 13.3% in those with N0, 20.9% in those with N1, and 55% in those with N2. It was observed that CA 19-9 positivity increased as the level increased.

The rate of CA 19-9 positivity in patients with metastases (80%) was statistically significantly higher than in patients without metastases (14.6%) (p: 0.000; p < 0.05). CA 19-9 positivity was observed in 21.5% of the women and 20.3% of the men, and there was no statistically significant difference between them (**Table 4**).

Table 4. CA 19-9 assessments by research parameters

	CA 19-9 Positive	CA 19-9 Negative	p
	n (%)	n (%)	
Location			[1]0.037*
Rectum	6 (11.5%)	46 (88.5%)	
Right	6 (17.1%)	29 (82.9%)	
Left	20 (30.3%)	46 (69.7%)	
Histological grade			[2]0.528
Grade 1	3 (18.8%)	13 (81.3%)	
Grade 2	26 (20.2%)	103 (79.8%)	
Grade 3	3 (37.5%)	5 (62.5%)	
Depth of invasion			[2]0.002*
T1	1 (10%)	9 (90%)	
T2	1 (4.3%)	22 (95.7%)	
T3	8 (13.3%)	52 (86.7%)	
T4	22 (36.7%)	38 (63.3%)	
TNM stage			[2]0.000*
Stage I	2(8%)	23(92%)	
Stage II	8(13%)	54(87%)	
Stage III	10(21.3%)	37(78.7%)	
Stage IV	32(63.2%)	7(36.8%)	
Lymphovascularinvasion			[3]0.000*
Negative	5 (7%)	66 (93%)	
Positive	27 (32.9%)	55 (67.1%)	
Perineural invasion			[3]0.001*
Negative	16 (14.2%)	97 (85.8%)	
Positive	16 (40%)	24 (60%)	
Lymph nodes			[1]0.000*
N0	12 (13.3%)	78 (86.7%)	
N1 (1-3 LN +)	9 (20.9%)	34 (79.1%)	
N2 (4 and above +)	11 (55%)	9 (45%)	
Metastases			[3]0.000*
Negative	20 (14.6%)	117 (85.4%)	
Positive	12 (80%)	3 (20%)	
Gender			[3]1.000
Female	15 (20.3%)	59 (79.7%)	
Male	17 (21.5%)	62 (78.5%)	

1Chi-Squared Test, 2 Fisher Freeman Halton Test, 3Continuity (yates) correction; T: Tumor; TNM: Tumor-LymphNode-Metastasis; CEA: Carcinoembriogenic antigen; CA 19-9: Carbohydrate antigen 19-9. CA 19-9 value of 35U/ml and above was considered positive.

DISCUSSION

Tumor markers are used to estimate prognosis, diagnoses and stage, classify the cancer, select an appropriate treatment, detect cancer residual disease, and assess the treatment process. Since tumor markers can be used to predict the response of a tumor to treatment and for prognosis, researchers believe that they might also be useful in screening tests that aim to detect cancer early before there are any symptoms. However, studies to determine whether circulating tumor markers can be used to screen for cancer have generally found that these markers are neither sensitive nor specific enough. When a test has low specificity, people must undergo further testing to determine whether cancer is present. Some screening tests based on tumor markers have been shown to lead to overdiagnosis, which happens when people are diagnosed with cancers that would never have affected them during their lifetimes.[12]

The median age of the 153 patients included in the present study was 64 years. The average age of diagnosis for CRC is 67 years, and it has been observed that patients are diagnosed and operated on at an earlier age in our country.

In a prospective study conducted with 333 patients by Yu et al., CEA positivity was found to be 33.6% and CA 19-9 positivity 18.3% in patients with CRC, and this rate was 35.3% for CEA and 20.9% for CA 19-9 in our study, which is compatible with the literature.[13]

In 1999, the American College of Pathologists' consensus statement reported preoperative CEA elevation as a Category 1 prognostic factor. For Category 1 factors, it has been stated that "It has been conclusively proven to have prognostic significance based on statistically robust evidence from multiple publications and is generally used in patient

management.".[14] However, at the time, preoperative CEA was the only Category 1 factor not included in the current American Joint Committee on Cancer (AJCC) staging system.[15] Later, according to the European Group on Tumor Markers (EGTM) guidelines, preoperative CEA was accepted as an independent prognostic indicator.[16] Other reports have suggested that advanced tumors are significantly associated with higher preoperative and postoperative CEA levels.

In our study, when the stages were compared with patients with positive CA 19-9 and CEA levels, it was observed that an increase in CA 19-9 was correlated with advanced stages, and this was statistically significant. In a study by Zheng et al.[17] investigating the prognostic value of CEA, CA 19-9, and CA 72-4 in patients with CRC, the Dukes stages of the patients and tumor marker values were examined, and it was found that the values of all three tumor markers increased statistically significantly in advanced stages. Yang et al.[18] also compared preoperative CEA and CA 19-9 values with tumor stages in a case–control study with CRC patients and found that tumor marker values increased when correlated with stage. Moreover, in Zheng et al.[17] case–control study, a significant correlation was found between CEA and CA 19-9 levels, depth of invasion, and number of positive lymph nodes. In our study, the rate of CA 19-9 positivity in T4 patients (36.7%) was significantly higher than in T1, T2, and T3 patients. The rate of CEA positivity according to the depth of tumor invasion was significantly higher in T4 patients (61.7%) than in T1, T2, and T3 patients. In addition, a significant association was found with lymphovascular and perineural invasion. In the same study, no statistically significant correlation was found between histologic grade, age, and gender. In a study by Tumay et al.[19] in which 315 CRC patients were followed up for 13 years after treatment, elevated CEA levels were found to be associated with advanced stage, depth of invasion, lymph node involvement, and tumor size, similar to our study.

Some studies have reported that CEA is informative in determining the prognosis of the disease independent of the cancer stage.[20-22] However, it has been reported that it can be used to determine the prognosis in Stage 2. Some studies have reported that CEA should be evaluated together with histopathologic parameters in newly diagnosed cases in order to determine which patients should receive adjuvant chemotherapy.[16,23,24] In our current study, we compared CEA and CA 19-9 levels with histopathologic features of the tumor and obtained similar results with depth of invasion, liver metastasis, and histologic type, similar to Sato et al.[25]

The presence of metastases is classified as Stage 4 in the TNM staging of CRC. In our study, the rate of CA 19-9 positivity in patients with metastasis (80%) was statistically significantly higher than that in patients without metastasis (14.6%), and the rate of CEA positivity in patients with metastasis (100%) was statistically significantly higher than that in patients without metastasis (28.5%), which is consistent with the literature.[13,25]

CONCLUSION

The following points summarize our findings and conclusions:

- The median age at diagnosis for CRC was 64 years. In Turkey, it is important to start screening programs from the age of 50 for those who do not have a first-degree relative with CRC in terms of early diagnosis of the disease.
- CEA and CA19-9 positivity is not statistically significant with gender and the histological grade of the tumor.
- CEA and CA 19-9 positivity rates increase as the depth of tumor invasion increases.
- In tumors with metastasis, lymphovascular and perineural invasion, and progression of lymph node involvement, the levels and positivity rates of the markers increase.
- Elevated CA 19-9 may be a predictor, especially for left-sided tumors.
- Tumor markers are significantly higher in older patients, suggesting that older patients are more important for screening than younger patients.

In light of this information, CEA and CA 19-9 are still valuable biomarkers in predicting advanced-stage tumors in our country. CRC is a deadly disease that must be screened in line with the recommendations of our Ministry of Health due to the financial and labor losses it causes. Our physicians should also refer patients with symptoms suggestive of CRC, such as rectal bleeding, changes in bowel habits, unexplained anemia, and a positive fecal occult blood test, especially those over the age of 50, to the relevant specialist for endoscopic imaging of the gastrointestinal tract. The retrospective nature of our study poses a problem in terms of sample size. We believe that multicenter, prospective, and larger patient-based studies regarding the prognostic importance of tumor markers in colorectal cancer are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziosmanpasa Taksim Training and Research Hospital Clinical Researches Ethics Committee (Date: 24.01.2018, Decision No: 130).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Evaluation of the Relationship Between Preoperative Patient Anxiety Level and Health Literacy

Preoperatif Hasta Anksiyete Düzeyleri ile Sağlık Okuryazarlığı Arasındaki İlişkinin Değerlendirilmesi

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Abstract

Aim: Sociodemographic characteristics such as age, gender, and educational status are factors associated with preoperative anxiety. Health literacy may be the influencing factor in different results obtained in various studies regarding the relationship between educational status and preoperative anxiety.

Material and Method: This prospective survey was carried out on 155 patients scheduled for elective surgery at the Department of Otorhinolaryngology between September and November 2019. Sociodemographic and basic health status data were recorded using the State-Trait Anxiety Inventory (STAI-I) and the Health Literacy Index (HLI).

Results: While there was statistically significant difference between average scores of the access, understanding and appraisal of health information subscales according to the HLI ($p<0.01$), no significant difference was found with average score of the application of health information subscale ($p>0.05$). A negative medium level relationship was found between average scores of the STAI-I and the HLI ($r=-0.424$) and application subscale ($r=-0.482$), and a negative low level relationship was found between the overall STAI-I and the access ($r=-0.335$), understanding ($r=-0.368$) and appraisal of health information ($r=-0.353$) subscales.

Conclusions: It was concluded that the low level of health literacy may be effective in the increased preoperative anxiety levels in patients, and further studies are required to be conducted in this matter.

Keywords: Anxiety, health literacy, educational status

Öz

Amaç: Yaş, cinsiyet, öğrenim düzeyi gibi sosyodemografik özellikler preoperatif anksiyete ile ilişkili faktörlerdir. Öğrenim düzeyi ile preoperatif anksiyete ilişkisinin çalışmalar arasında farklılık göstermesinde sağlık okuryazarlığı etkili olabilir.

Gereç ve Yöntem: Kesitsel türdeki bu anket çalışması, Eylül-Kasım 2019 tarihleri arasında Kulak Burun Boğaz Bölümü'nde elektif operasyon planlanan 155 hasta üzerinde gerçekleştirildi. Hastalara Durumluk Kaygı Ölçeği (STAI-D) ile Sağlık Okuryazarlığı Ölçeği (SOYÖ) uygulanarak, sosyodemografik ve temel sağlık durumu ile ilgili veriler kaydedildi.

Bulgular: Eğitim durumlarına göre SOYÖ ile bilgiye erişim, bilgiyi anlama ve değer biçme alt boyutu puan ortalamalarında istatistiksel açıdan anlamlı bir fark olduğu saptanırken ($p<0,01$), uygulama alt boyutu puan ortalamasında anlamlı fark tespit edilmedi ($p>0,05$). STAI-D ile SOYÖ ($r=-0,424$) ve uygulama alt boyutu ($r=-0,482$) puan ortalamaları arasında negatif yönde orta düzeyli bir ilişki ve STAI-D ölçeği ile bilgiye erişim ($r=-0,335$), bilgiyi anlama ($r=-0,368$) ve değer biçme ($r=-0,353$) alt boyutları arasında negatif yönde düşük düzeyli bir ilişki olduğu tespit edildi.

Sonuç: Preoperatif anksiyete düzeyindeki artışta düşük sağlık okuryazarlığı seviyesi etkili olabilir. Bu konuda daha ileri çalışmaların yapılması önerilir.

Anahtar Kelimeler: Anksiyete, sağlık okuryazarlığı, öğrenim düzeyi

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INTRODUCTION

Anxiety is a natural reaction that an individual develops to circumstances in which they do not feel safe. The level of anxiety during the preoperative period may be affected by various sociodemographic factors such as patients' age, gender, marital status and educational status.[1] There are studies indicating that educational status has positive or negative effects on anxiety, while it was considered ineffective in some studies.[2,3]

Health literacy is defined as the level of ability to obtain, process, and understand basic health information in order to make health decisions.[4] In many studies, it was found that the level of health literacy among university graduates is higher than that of high school and primary school graduates.[5] However, it is a concept influenced by many factors and, contrary to what is expected, those who have high level of education may have low levels of health literacy.[6]

When the literature was reviewed, no studies were found investigating the relationship between preoperative anxiety and health literacy. In this study, it was aimed to evaluate the effect of health literacy on preoperative anxiety, and to reveal the relationship between demographic factors, educational status and basic health status.

MATERIAL AND METHOD

This prospective survey was conducted between September and November 2019 to determine the relationship between the level of health literacy and anxiety and educational status of perioperative patients in accordance with the Declaration of Helsinki. Prior to the study, ethical approval was received from the ethics committee of Necmettin Erbakan University Faculty of Medicine (Date: 13.09.2019, Decision Number: 2019/2041).

The sample of the study consisted of patients aged between 18 and 65, who were to undergo elective surgery at Department of Otorhinolaryngology, and were ASA (American Society of Anesthesiology) I and II. 155 patients who were at least primary school graduates and capable of fully understand the questions were included the study after obtaining written informed consent. Those who were illiterate, non-consenting, pregnant, with mental and/or central nervous system pathology and malignancy, and those in ASA III and IV groups were excluded from the study.

The data were collected through face-to-face interviews and three-parts questionnaire was applied. First part of the form included data on the demographic and basic health status of patients , the second part included the State-Trait Anxiety Inventory (STAI-I) to assess preoperative anxiety levels, and the third part included the Health Literacy Index (HLI) to determine health literacy levels.

State-Trait Anxiety Inventory (STAI) includes state and trait anxiety subscales and developed by Spielberger. The State Anxiety Inventory (STAI-I) is used to evaluate the preoperative anxiety levels of the patients.There are 20 items on both tests, score changes between 20-80.[7]

Health Literacy Scale (HLS); includes 25 items and 4 subscales (access, understand, appraise and apply). Questionnaire type is likert and score changes between 25-125.[8] The higher score means the higher health literacy level.[9]

The sample size of the study was calculated based on the mean STAI-1 score (38.0 ± 9.9) reported in the study by Erkılıç et al., and based on the STAI-1 score (42.72 ± 9.84) reported by Akınsulore et al. The G*Power 3.1 Program was used for the sample size calculation.[10,11] As a result of the analysis carried out at a 90% confidence level with a margin of error equal to 0.05, the effect size 0.48, the sample size was found to be 152. A total of 155 patients were included in the study. While evaluating the findings obtained in the study, SPSS 22.0 Statistical package program was used for statistical analyses. Skewness and Kurtosis values were examined to assess the normal distribution of the data, and the data were found to normally distributed since the values were found to range between +1 and -1. In this context, independent samples t-test, one-way analysis of variance (ANOVA) and linear regression analysis was used for data analysis in addition to descriptive statistics. The research findings were evaluated at a confidence interval of 95% and significance level of $p<0.05$.

RESULTS

The average age of the participants was 36.61±13.94 years, of which 63.2% were male and 67.1% were married. While 33.5% of the participants were primary school graduates, 37.3% held college or university degrees. **Table 1** shows STAI-I Comparison analyzes by demographic data.

Table 2 shows Demographic Data and Main Health Variables with Comparative Analysis of the STAI-I and the HLI. While statistically significant difference was found between average scores of the HLI and access, understanding and appraisal subscales in accordance with educational status ($p<0,01$), no statistically significant difference was found with average score of the application subscale ($p>0,05$). According to the Scheffe Test, one of the post hoc tests applied to determine which groups lead to the significant difference between average scores, the scores of the college-university group were found to be significantly higher.

There was a negative medium level correlation between the average scores of the STAI-I and the HLI (r=-0,424) and application subscale (r=-0,482), while a negative low level correlation was found between the STAI-I and the access (r=-0,335), understanding (r=-0,368) and appraisal of health information (r=-0,353) subscales. It can be concluded that as the average STAI-I score of the participants increases, average scores of the HLI and its subscales decrease.

Table 1: STAI-I Comparison analyzes by demographic data

Variables (n=155)	n	Avg.±Sd.	t / F	p
Gender			-1.944	0.054
Male	98	37.19±8.07		
Female	57	39.75±7.62		
Marital Status			0.188	0.851
Married	104	38.21±8.71		
Single	51	37.98±6.31		
Educational Status			0.224	0.879
Primary School 1	55	38.73±8.95		
Middle School 2	18	37.06±6.03		
High School 3	35	38.11±8.58		
University 4	47	37.87±7.09		
Occupation			2.197	0.091
Government Official 1	32	37.84±8.23		
Self-Employed 2	51	36.57±8.28		
Unemployed 3	39	40.79±7.39		
Other 4	33	37.70±7.48		
Smoking Status			0.430	0.668
Non-smoker	99	38.34±7.30		
Smoker	56	37.77±9.11		
ASA			-0.953	0.342
ASA I	59	37.36±6.92		
ASA II	96	38.61±8.57		
Additional Disease			-2.119	0.036
Yes	112	37.30±7.80		
No	43	40.30±8.13		
Scheduled Operation			0.340	0.796
Cosmetic rhinoplasty1	25	36.96±5.76		
Functional rhinoplasty2	62	38.52±8.66		
Tympanoplasty 3	42	38.67±7.98		
Other 4	26	37.50±8.38		
Previus Surgery			1.037	0.301
Yes	97	38.62±7.33		
No	58	37.28±8.97		

STAI : State- Trait Inventory, ASA: American Society of Anesthesiology, t/F : Independent samples t test/ Analysis of Variance

Table 2. Demographic Data and Main Health Variables with Comparative Analysis of the STAI-I and the HLI

Scales	Avg.±Sd.	Min	Max	Cronbach's Alpha
STAI-I	38.14±7.98	22.00	64.00	0.87
HLI (Overall score)	89.18±19.20	41.00	125.00	0.96
Subscales				
Access	18.53±4.64	7.00	25.00	0.92
Understanding	23.62±6.06	10.00	35.00	0.88
Appraisal	28.32±6.79	11.00	40.00	0.90
Application	18.72±4.07	9.00	25.00	0.83

* STAI : State- Trait Inventory, HLI : Health Literacy Index

The regression analysis conducted between the average HLI scores and its subscales and the STAI-I was given in the **Table 3**. The analysis performed between the HLI and the STAI-I was found to be statistically significant (p<0.001). 18% of the variance in the STAI-I is explained by the HLI (R2=0,18). The variance in the HLI is negatively reflected in average score of the STAI-I. The analysis conducted between the access, understanding, appraisal, and application of health information subscales of the HLI and the STAI-I was found to be statistically significant (p<0.001). 23% of the variance in the STAI-I is explained by the application of health information subscale (R2=0,23). The variance in the application of health information subscale is negatively reflected in the average score of the STAI-I.

Table 3: Regression Analysis between STAI-I and HLI

Dependent variable	Independent variable	B	sh	T	F	p	R2
STAI-I	State	53.84	2.77	19.41	33.54	<0.001	0.18
	HLI (overall score)	-0.18	0.04	-5.79			
STAI-I	State	48.81	2.50	19.51	19.35	<0.001	0.12
	Access	-0.58	0.13	-4.40			
STAI-I	State	49.58	2.41	20.55	23.99	<0.001	0.13
	Understanding	-0.48	0.09	-4.89			
STAI-I	State	49.88	2.59	19.27	21.78	<0.001	0.12
	Appraisal	-0.41	0.09	-4.67			
STAI-I	State	55.83	2.66	20.99	46.36	<0.001	0.23
	Application	-0.94	0.14	-6.81			

*B: Beta, se: Standard error, T: Independent samples t test, F: Analysis of Variance

DISCUSSION

Although the STAI-I threshold used in case of clinically significant anxiety ranges between 39 and 40, while it varies between 36 and 45 in different studies conducted in preoperative patients.[12-14] In the current study, the mean±SD STAI-I scores of preoperative patients was found 38.14±7.98. The participants obtained an average score of 89.18±19.20 from the HLI, while it was 18.53±4.64 for access of health information, 23.62±6.06 for understanding of health information, 28.32±6.79 for appraisal of health information, and 18.72±4.07 for application of health information, which are consistent with the literature.[8]

While most studies have shown that preoperative anxiety levels are higher in women, there are also studies that report no relationship according to gender.[15-17] In these studies, it has been stated that this difference between women and men may be related to the fact that women are more comfortable expressing their concerns, and are more anxious due to separation from family members.

Although the majority of studies indicate that there is no relationship between age and preoperative anxiety level, it has been found that the level of health literacy decreases as age increases.[15,16,18] Decreased level of health literacy with increased age may be associated with conditions such as low educational level of older people, decline in cognitive abilities, and the inability to closely follow developments.

Regarding the relationship between preoperative anxiety and additional diseases, studies found that patients with chronic diseases had higher levels of anxiety or there was no relationship; however, contrary to the literature, the current study determined that those without additional diseases obtained significantly higher average scores from the STAI-I compared to others.[3,6] This may be explained by the fact that

patients with chronic diseases develop the ability to accept their illness and cope with it, which leads to a positive perception on anxiety. When the relationship between health literacy and additional diseases was examined, numerous studies found that those with additional diseases had lower levels of health literacy.[18,19] In this study, no significant difference was found between average scores of the HLI and its subscales according to the status of having additional diseases ($p>0.05$). While most studies associated lower level of health literacy of people with additional diseases with their old age and low educational level, no significant difference was found in this study; which can be associated with the fact that our study population has a lower average age and no additional diseases.

There are studies indicate that anxiety scores of the group without previous anesthesia experience are higher than those experienced it, or there is no relationship.[12,17,21] In this study, it was found that there was no statistically significant difference between the average preoperative anxiety scores and previous surgery. While there was no significant difference between the HLI and access, understanding and appraisal of health information subscales according to previous surgery, a statistically significant difference was found in the average score of application of health information subscale, and those who previously underwent surgery were found to obtain higher average scores. Consistent with other statistical data in our study, this may be associated with the fact that the application of health information subscale may be related to individuals' experiences rather than their level of education.

In some studies, it was found that people with higher level of education had higher levels of preoperative anxiety.[2,12,14,15,21,22] This result was explained by the fact that as the level of education of patients increased, their awareness of the risks of anesthesia and surgery increased, and that these individuals were more capable of expressing their anxiety.[21] However, individuals with a high level of education are expected to research more and be able to cope with stress more comfortably since they have higher knowledge. On the contrary, there are also studies indicating that there is no relationship between educational status and preoperative anxiety.[22,23] In the current study, there was no statistically significant difference between educational status and anxiety. In most of the studies evaluating the relationship between health literacy and educational status, it is stated that as the level of education of individuals increases, the level of health literacy also increases.[4,24-29] However, health literacy is a concept influenced by many factors and, contrary to what is expected, people with higher level of education may have low level of health literacy.[6] Although there are more studies indicating a positive correlation between educational status and health literacy, it is not an absolute requirement that higher educated individuals would have higher levels of health literacy.[30] This is associated with the fact that educational status is not the only determinant of the health literacy level. In the study, it was concluded that there was a statistically significant difference in average scores of the participants obtained from the HLI and accessing, understanding and appraisal of health information subscales according to their educational status, while there was no significant difference in average score of the application of health information subscale. Therefore, the ability of patients to make informed decisions about medical issues and to reflect opinions on health-related issues are not directly related to their educational background. As well as experiences, interests, interest in general cultural activities such as reading books or going to the movies; the strength of one's will may also be related to their ability to do what is needed for their own health.

The variance in the HLI and all subscales is negatively reflected in the average STAI-I scores. In the study, the most effective HLI subscale on the average score of STAI-I was application of health information subscale, and no statistical difference was found with the educational status of the patients. This finding may also be explained by the fact that there is no direct relationship between educational status and preoperative anxiety, or that there are different findings in the literature.

In the study, the relationship between health literacy and preoperative anxiety is revealed more decisively than the educational status. This result can also be considered as the effect of decreased level of preoperative anxiety related to educational status as well as its effect on health literacy; since people with high educational level obtained higher scores in other subscales except for application of health information in this study. However, the fact that the application subscale was the most effective subscale on preoperative anxiety, and that it was not found to be related to educational status may be interpreted that the level of education does not always lead to a positive effect on preoperative anxiety.

We consider that the effect of educational status on preoperative anxiety is due to the positive effect it has on health literacy. That is because, although three of four subscales of the HLI were related to education, the application of health information subscale was the most effective subscale on preoperative anxiety despite the fact that it was independent of the educational status.

High level of preoperative anxiety in individuals with low level of health literacy may be associated with the fact that since patients are more capable of accessing and understanding health information as well as interpreting and evaluating it during the preoperative period, they manage the situation more comprehensively and be actively involved throughout the process.

CONCLUSIONS

There are different results in the literature regarding the relationship between preoperative anxiety levels and educational status, and a consensus on the issue has not been reached. There is also no decisive agreement on the relationship between health literacy and educational status. In addition, although people have a similar level of education, their reading, writing, comprehension and calculation skills may vary. Therefore, it is stated that the level of health literacy should be taken into consideration when evaluating an individual about health-related issues, rather than solely focusing on their educational status (31). The effect of educational status on preoperative anxiety may actually be due

to its effect on the level of health literacy. The most important reason for this conclusion is that the relationship between educational status and preoperative anxiety was found to vary in different ranges in the literature. In the light of the above information, it has been considered that it is appropriate to evaluate health literacy rather than the educational status when examining preoperative anxiety levels; however, more studies are needed to examine the relationship between health literacy and educational status and preoperative anxiety.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Necmettin Erbakan University Faculty of Medicine (Date: 13.09.2019, Decision Number: 2019/2041).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Orthopedic Evaluation of Skiing Injuries in Erzurum Palandoken Ski Center

Erzurum Palandöken Kayak Merkezi Kayak Yaralanmalarının Ortopedik Açıdan Değerlendirilmesi

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Abstract

Aim: To determine the demographic and clinical characteristics of patients who presented to our emergency department with orthopedic injuries due to winter sports.

Material and Method: This study was retrospectively conducted in the winter seasons between 2018 and 2020. The patients' age, gender, orthopedic injury localization, treatment applied for the injury, and injury patterns were examined. The findings obtained were statistically analyzed.

Results: In this study, a total of 881 patients, 311 (35.4%) female and 570 (64.6%) male, were evaluated. According to orthopedic localization, most patients (n=255, 28.6%) had knee injuries. Soft tissue trauma was detected in 519 (58.9%) of the patients. The knee injuries did not significantly differ according to gender (p=0.852).

Conclusion: During winter sports, injuries occur mostly in the lower extremity and knee area. Injuries related to winter sports can be reduced with the use of appropriate winter sports equipment and ski training.

Keywords: Winter sports, skiing, snowboarding, sports injuries, trauma

Öz

Amaç: Bu çalışmada kış sporları nedeni ile ortopedik yaralanması olup acil servisimize başvuran hastaların demografik ve klinik özelliklerini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu çalışma 2018-2020 tarihleri arasında kış sezonunda retrospektif olarak yapıldı. Hastaların yaş, cinsiyet, ortopedik yaralanma bölgesi, yaralanmasına yönelik tedavileri, yaralanma şekilleri incelendi. Elde edilen bulgular istatistiksel olarak analiz edildi.

Bulgular: Çalışmamızda n:311 (35.4%) kadın ve n:570 (64.6%) erkek hasta olmak üzere toplam 881 hasta değerlendirildi. Ortopedik lokalizasyonuna göre hastalarda 255(%28.6)', en fazla diz yaralanması tespit edildi. Hastaların 519 (%58.9)'una yumuşak doku travması tanısı konuldu. Diz yaralanmasının cinsiyetlere göre farkı yoktu (p=0.852).

Sonuç: Kış sporu yaralanmalarında en fazla alt ektremite ve diz bölgesinde yaralanma olmaktadır. Uygun kış sporu ekipmanlarının kullanılması ve kayak eğitimlerinin alınması ile kış sporlarında yaralanmaları azaltabiliriz.

Anahtar Kelimeler: Kış sporları, kayak, snowboard, spor yaralanmaları, travma

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INTRODUCTION

Winter sports are one of the sports activities with an increasing prevalence across the world. Skiing, sledding, and snowboarding are popular winter sports.[1] Due to their fast nature, they involve a risk of injury. As the number of people engaged in winter sports increases, the rate of presentation to health institutions due to related injuries also increases, but the exact number remains unclear.[2] According to the European Injury Data Base, every year, 300,000 skiers and snowboarders are treated for injuries in Europe, which has a population of 500 million.[3]

Skiers in winter sports can injure not only themselves but also those skiing around them. The reasons for this include skiing experience, unknown track, and non-personalized ski equipment.[4] The most common cause of skiing injuries is falling. As a result, lower extremity, upper extremity, vertebral, and head traumas are frequently seen in these patients.[5,6]

In this study, we aimed to determine the demographic and clinical characteristics of patients who presented to our emergency department with orthopedic injuries due to winter sports in Palandoken Ski Center over three winter seasons.

MATERIAL AND METHOD

This study was retrospectively conducted in the winter seasons between 01.11.2018 and 31.03.2020. The clinical research ethics committee of Erzurum Regional Training and Research Hospital committee approved the study on 11/04/2022 with the approval number E-37732058-514.99.

All individuals with winter sports injuries, who were aged over five years and were not pregnant, were included in the study. The same patient's ski injury at different times was also included in the study. Patients without orthopedic injuries were excluded from the study. At the time of the study, Palandoken Ski Center consisted of four tracks. It was determined that a total of 224,657 people stayed in the accommodation facilities within the center and used the ski tracks over the three winter seasons. However, the number of patients using the track facilities in a day could not be determined. During the same period, a total of 962 patients visited the emergency department due to winter sports injuries. Eighty-one of these patients had no orthopedic injury, and therefore were excluded from the study. The remaining 881 patients with orthopedic injuries were included in the sample.

Patients that presented to the emergency department were screened through the hospital automation system and patient files. Those with the same identity information according to both records were considered as a single presentation. The patients' age, gender, localization of orthopedic injury, treatments applied, and mode of injuries were recorded. The pathologies were categorized into eight different sites according to their orthopedic localization: knee, shoulder, hand-wrist, foot-ankle, pelvis-hip, vertebra, elbow, and forearm. The mode of injury was evaluated as falling or hitting.

Statistical analysis was performed using SPSS software version 25.0 (IBM Corp., Armonk, New York, USA). The distribution of variables was evaluated for normality using the Kolmogorov-Smirnov test. Descriptive statistics were given as frequency (n) and percentage (%) values for categorical variables. For 2×2 comparisons between categorical variables, the Pearson chi-square test was used if the expected value was >5, the chi-square Yates test if 3-5, and Fisher's exact test if <3. For comparisons greater than 2×2 between categorical variables, the Pearson chi-square test was used when the expected value was >5 and the Fisher-Freeman-Halton test when it was <5. The statistical significance level was taken as $p<0.05$.

RESULTS

A total of 881 patients, 311 (35.4%) female and 570 (64.6%) male, were included in the study. The median age of the patients was 29.4 (minimum: 5-maximum: 67) years. Of the patients, 695 (77.8%) had been injured when skiing and 186 (21.2%) when snowboarding. The remaining demographic data of the patients are detailed in **Table 1**.

When the pathologies were categorized according to their orthopedic localization, knee injuries were most common, detected in 252 (28.6%) patients. This was followed by hand-wrist injuries in 247 (28.0%) patients, shoulder injuries in 132 (15.0%), foot-ankle injuries in 100 (11.3%), pelvis-hip injuries in 55 (6.2%), vertebral injuries in 39 (4.4%), elbow injuries in 35 (4.1%), and forearm injuries in 21 (2.4%) (**Table 1**).

When the diagnoses of the patients were evaluated, 519 (58.9%) patients were diagnosed with soft tissue trauma, 328 (37.2%) with bone fractures, and 34 (3.9%) with joint dislocation (**Table 1**).

Simple non-invasive treatments were performed in 740 (83.9%) patients with orthopedic injuries. Dressing was applied to 47 (5.3%) patients, plaster-splint to 263 (29.9%) patients, bandage to 147 (16.6%) patients, and medical treatment to 283 (32.1%) patients. Surgical treatment was undertaken in 141 (16.1%) patients after necessary interventions (**Table 1**). According to orthopedic localization, hand-wrist injuries most required surgical treatment (n=28, 19.8%).

When the orthopedic injury sites were evaluated according to gender, 83 women and 169 men had knee injuries, with no statistically significant difference between the two groups (p=0.852). There were hand-wrist injuries in 80 women and 167 men, indicating no statistically significant difference according to gender (p=0.846). There was also no gender difference in the remaining orthopedic injury regions (**Table 2**).

Table 1: Patients' demographic characteristics

Variables	n=881 (100%)
Age (median, min-max)	29.4 (5-67)
Gender	
Female	311 (35.4)
Male	570 (64.6)
Time of injury	
08:00-12:00 hours	118 (13.2)
12:01-16:00 hours	399 (45.3)
16:01-20:00 hours	346 (39.6)
20:01-07:59 hours	18 (1.9)
Injury month	
December	101 (11.5)
January	152 (17.3)
February	425 (48.2)
March	203 (23.0)
Type of winter sport	
Ski	695 (77.8)
Snowboard	186 (21.2)
Injury site	
Knee	252 (28.6)
Hand-wrist	247 (28.0)
Shoulder	132 (15.0)
Foot-ankle	100 (11.3)
Pelvis-hip	55 (6.2)
Vertebra	39 (4.4)
Elbow	35 (4.1)
Forearm	21 (2.4)
Diagnosis	
Soft tissue trauma	519 (58.9)
Bone fracture	328 (37.2)
Joint dislocation	34 (3.9)
Treatment applied	
Dressing	47 (5.3)
Plaster-splint	263 (29.9)
Bandage	147 (16.6)
Medical treatment	283 (32.1)
Surgery	141 (16.1)

Table 2: Evaluation of injury sites by gender

Injury site	Female (n=311)	Male (n=570)	p
Knee	83	169	0.852
Hand-wrist	80	167	0.846
Shoulder	47	85	0.286
Foot-ankle	37	63	0.542
Pelvis-hip	15	40	0.652
Vertebra	14	25	0.147
Elbow	12	23	0.185
Forearm	8	13	0.252

DISCUSSION

In this study, patients with orthopedic injuries who presented to the emergency department with winter sports injuries were evaluated according to epidemiology and injury sites. It was determined that 224,657 people stayed at the Palandoken Ski Center over the three winter seasons, and 962 (0.42%) people were injured. Orthopedic injuries were detected in 881 (91.5%) of these patients. When the literature is examined, the incidence of injuries related to winter sports is reported to be approximately 2-3%.[7-9] In our study, injuries were detected in 0.42% of the individuals using the accommodation facilities of the ski center. We consider that this lower rate in our study is related to these facilities also being used by holidaymakers that do not engage in winter sports.

According to the literature, there is no significant difference between genders in terms of injuries in individuals exposed to skiing injuries; however, the rate of injuries is higher in men.[10,11] In a study conducted in Finland, 35 (57.4%) of the patients with skiing injuries were found to be male, and 25 (42.6%) female.[10] In our study, similar to the literature, orthopedic injuries were more common in men.

Falls are the most common cause of injury when skiing due to various factors, such as uneven ground, melted or icy snow, and speed. In the literature, the most common cause of injury in skiing has been reported as falling.[12,13] In our study, we also determined that the mode of injury was mostly falling. We consider that this is related to not only the characteristics of the track but also the skiing experience of individuals.

Studies have reported that more than 50% of winter sports injuries involve the lower extremity, followed by the upper extremity.[10-12,14] This has been attributed to the lower extremity being under the control of the ski, board, or sled during winter sports activities, and thus being exposed to more physical stress.[13] In a study conducted by Gür et al., the rates of upper and lower extremity injuries were determined as 31.9% and 30.9% respectively among individuals engaging in winter sports.[15] In our study, the most orthopedic injury localization was found to be the lower extremity, and the most common site of injury was the knee.

In most studies, it has been stated that fractures and sprains mostly occur as a result of skiing injuries in individuals performing winter sports.[16,17] In a study conducted in Antarctica, Cattermole et al. reported that the most common type of injury was sprains with a rate of 62.7%, while the rate of fractures remained at the level of 15%.[18] In another study, Gür et al. determined that 55% of patients with winter sports injuries were diagnosed with soft tissue trauma and 33.5% with fractures.[15] In the current study, similar to the literature, soft tissue trauma was the most common diagnosis, followed by bone fractures.

Limitations

Among the limitations of the study are the inclusion of only orthopedic injuries in the sample and absence of the evaluation of other pathologies in winter sports injuries. Another limitation is that the study was conducted in a single center.

CONCLUSION

Most winter sports injuries affect the lower extremity and knee region. Winter sports injuries can be reduced with the use of appropriate equipment and ski training.

ETHICAL DECLARATIONS

Ethics Committee Approval: The clinical research ethics committee of Erzurum Regional Training and Research Hospital committee approved the study on 11/04/2022 with the approval number E-37732058-514.99.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Relationship of Pro-BNP Levels with Cardiovascular Events in Pediatric Cardiac and Non-cardiac Diseases

Pediyatrik Kardiyak ve Nonkardiyak Hastalıklarda Pro-BNP Düzeyi ile Kardiyovasküler Olayların İlişkisi

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Abstract

Aim: We aimed to determine the relationship of Pro-BNP levels, with the diagnosis, clinical, and laboratory parameters in children. In addition, the predictive power of the Pro-BNP levels in determining the cardiovascular events was evaluated.

Material and Method: This study comprised 829 patients whose levels of Pro-BNP were measured. The data were obtained retrospectively from the hospital records. The relationship of the Pro-BNP level of the patients with the clinical, laboratory, and echocardiographic data was determined. The predictive power of the Pro-BNP and Troponin T levels in determining the development of cardiovascular events was evaluated.

Results: Cardiovascular events developed in 143 patients during the follow-up period. The Pro-BNP levels were observed to be significantly higher ($p< 0.001$) in the group in which patients developed cardiovascular events. The Pro-BNP levels demonstrated a positive correlation with both Troponin T levels and procalcitonin levels and a strong negative correlation with the age, height, and weight of the patients. The most important predictive factors for determining the development of cardiovascular events were the presence of tachypnea, increased Pro-BNP levels, increased left ventricular end-diastolic diameter, and increased tricuspid regurgitation velocity.

Conclusion: The most important determinants of a cardiovascular event, as revealed in the present study, are the presence of tachypnea, Pro-BNP levels, TR velocity, and the LVEDD z-score of patients. Moreover, the Pro-BNP levels and Troponin levels demonstrate a strong positive correlation. Randomized prospective studies are warranted to improve the efficacy of using Pro-BNP in differentiating cardiac and non-cardiac diseases in children.

Keywords: Brain natriuretic peptide, congenital heart disease, sepsis, troponin T

Öz

Amaç: Bu çalışmada amacımız Pro- BNP düzeyi ile hastaların tanıları, klinik ve laboratuvar bulguları arasındaki ilişkiyi değerlendirmektir. Ayrıca pro-BNP düzeyinin kardiyovasküler olay belirlemedeki öngörü düzeyini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışmada, Pro-BNP düzeyi bakılmış olan 829 hastanın verileri elektronik dosya kayıtlarından retrospektif olarak elde edildi. Pro-BNP düzeyi ile hastaların klinik, laboratuvar ve ekokardiyografik verileri rasındaki ilişki değerlendirildi. Ayrıca Pro-BNP ve troponin T düzeylerinin kardiyovasküler olayları belirleyiciliği değerlendirildi.

Bulgular: Takip süresi oyunca 143 hastada kardiyovasküler olay gelişti. Pro-BNP seviyesi bu hasta grubunda anlamlı yüksekti ($p< 0,001$). Pro-BNP düzeyi ile troponin T, prokalsitonin düzeyi ile pozitif, yaş, boy ve vücut ağırlığı ile güçlü negatif korelasyon mevcuttu. Kardiyovasküler olay belirlemede en güçlü prediktörler takipne, artmış Pro- BNP, artmış triküspit kapak velositesi ve artmış sol ventrikül end-diyastolik çapı idi.

Sonuç: Bu çalışmada kardiyovasküler olay belirlemede en güçlü belirleyiciler takipne, Pro-BNP düzeyi, triküspit yetersizlik velositesi ve sol ventrikül end-diyastolik çapı Z skoru idi. Ayrıca pro-BNP ve Troponin T düzeyleri arasında güçlü pozitif korelasyon mevcuttu. Çocuklarda kardiyak ve nonkardiyak hastalıkların ayırımında pro-BNP düzeyi belirleyiciliği düşük bulunmuş olup, randomize prospektif kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Beyin natriüretrik peptid, konjenital kalp hastalığı, sepsis, troponin T

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INTRODUCTION

B-type natriuretic peptide (BNP) is a peptide containing 32 amino acids and is secreted by the cells in the heart and the brain. The end-diastolic pressure and increased ventricular wall strain are the main triggers for BNP release.[1] The guidelines suggest a class 1 recommendation for the use of BNP in the diagnosis, differential diagnosis, and follow-up of adult patients.[2] Additionally, it is advised (class 2b) for pediatric heart disease diagnosis and follow-up.[3,4] Although the use of BNP in pediatric patients is growing nowadays because of its cost and convenience, there are still several restrictions on its use in children, such as the large variety of cardiac and non-cardiac disorders that can lead to heart failure.[5] The typical BNP range in children varies with age.[6] Numerous studies claim that the BNP levels, which are known to rise for a variety of causes, are inversely correlated with the clinical severity of pediatric heart failure.[7-11] BNP may also help distinguish between disorders that are cardiac and non-cardiac disease.[12]

Although there is evidence in support of the use of BNP in the diagnosis of heart failure in children, the differentiation of cardiac caused from the non-cardiac ones, the follow-up treatment, and prognosis determination, no consensus has been reached so far on the situations in which the use of BNP is recommended.[5] However, several studies have been conducted to compare specific diagnostic groups with healthy controls. A few of these studies also compared the factors underlying Pro-BNP elevation and Pro-BNP data among different diagnostic groups. The main goal of the current study was to determine whether there were any significant differences in the illness groups based on the Pro-BNP levels. In addition, the relationship of the Pro-BNP levels with the clinical and other laboratory data of the patients and the predictive power of these levels in determining the development of cardiovascular event (CVE) were evaluated.

MATERIAL AND METHOD

The current study included all patients who were less than 18 years old and who had Pro-BNP testing done in our institution between March 2014, and March 2020. Patients who were newborns and had heart surgery were excluded. The patient's age, height, weight, symptoms, physical examination findings, hemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, serum albumin, troponin T, procalcitonin level, C-reactive protein (CRP), culture results, electrocardiography, echocardiography, and chest X-ray. Data on the final diagnosis, CVE, history, mortality, and length of hospital stay were obtained from hospital records. We investigated the correlations between pro-BNP levels and CVE (surgery, arrhythmia, severe heart failure, interventional cardiac procedure, repeated hospitalization, and mortality). Eskişehir Osmangazi University non-interventional researches ethics committee approval was obtained (2020-181, 25403353-050.99-E.52038).

Statistical Analysis

The IBM SPSS package software was used to statistically analysis. The homogeneity of the quantitative variables to the normal distribution according to the groups was evaluated using the Shapiro–Wilk test. The t-test was used to compare the two groups for variables with normally distributed data, and the Mann-Whitney U test was used for variables with non-normally distributed data. The Kruskal- Wallis test was used to compare groups of three or more. By using Spearman's correlation analysis, the factors' associations with the CVE were established. Multivariate logistic regression analysis was adopted to evaluate independent risk factors related to cardiovascular event. The specificity and sensitivity values for Pro-BNP utilized at the levels were assessed using the ROC analysis. Pro-BNP was utilized at levels of 350pg/mL and 1701pg/mL and Troponin T was used at normal threshold values (0-0.014 ng/ml) in the Ross clinical scoring for assessing the CVE were evaluated using the ROC analysis to determine their specificity and sensitivity values.

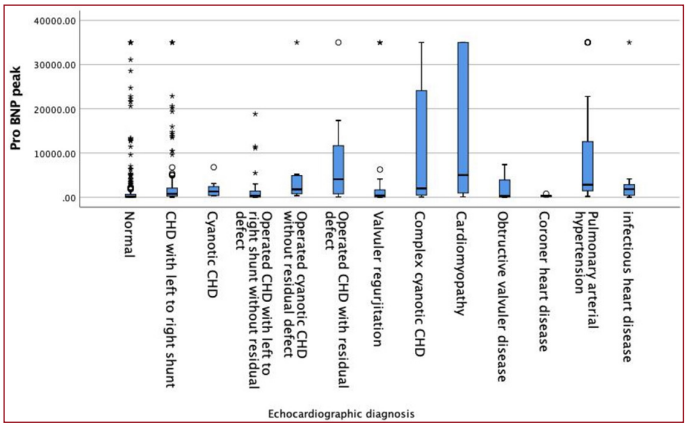
RESULTS

A total of 829 patients who had undergone pro-BNP examination between March 2014 and March 2020 were included in the present study, 397 (47.9%) of them were male. The median age was 84.72 months (1-251), median height was 110.64 cm (44-184), mean weight was 27.42 kg (1.32-112), and median duration of stay in the hospital was 6.19 days (0–76). The mean follow-up was 26± 18 months. In the 629 (75.2%) patients for whom the echocardiographic data were available, the left ventricular end-diastolic diameter (LVEDd) z score was 0.79 (-3.02 to +9.56) and the median tricuspid valve regurgitation velocity was 2.14 m/s (1- 5.4). The median peak Pro-BNP level was 3205.7 pg/mL (1.98–35000), while the minimum level was 4330.34 pg/mL (6.45–35000) in the patients with repeated measurements; the time interval between the minimum and maximum levels was 6.29 days (0.25–40). The median levels for troponin T, CRP, procalcitonin, hemoglobin, hematocrit, ALT, AST, serum creatinine, and serum albumin were 0.069 ng/mL (0.00-3.3), 4.28 mg/L (0-134.2), 3.33ng/mL(0-100), 12.08 gr/mL(5.7-19.9), 12.08% (5.7%–19.9%), 27.8 IU/L (2–1207), 46.5 IU/L (8–5582), 0.61 mg/dL (0.04–13.11), and 3.97 gr/dL (0.53–5.7), respectively.

A total of 338 (40.7%) of the patients were hospitalized; of these, 99 (11.9%) were admitted to the pediatric intensive care unit, 157 (18.9%) to the pediatric emergency service, 143 (17.2%) to the pediatric cardiology outpatient clinic, and 11.3% to other outpatient clinics for follow-up. Inpatient units were shown to have higher pro-BNP levels than outpatient units (inpatient units median= 665.45 pg/mL (min-max: 5- 35000); outpatient unit median: 78.84 pg/mL (min-max: 1.98- 35000; p< 0.0001).

The most common causes of pro-BNP detection were underlying congenital heart disease in 23.2% of patients and

other cardiac conditions in 40% of patients. The additional symptoms included respiratory distress, illnesses including acute and chronic renal failure that can lead to volume overload. Twenty three percent of patients had tachypnea, 20% had tachycardia, and 14% had fever, as determined by the physical exam. There were 629 individuals who had transthoracic echocardiography, and 290 of them had normal echocardiographic findings. **Graph 1** shows the pro-BNP levels and echocardiographic abnormalities. When the pro-BNP levels of the patients with volume and pressure load were compared according to their echocardiographic diagnosis, no significant difference was found (median, min-max 827 (6.48-36000), 1369 (11.17-35000) pg/ml, respectively).



Graph 1. Pro-BNP levels according to echocardiographic diagnosis groups
CHD: Congenital heart disease

Electrocardiographic pathology was detected in 39 of 652 patients (5.9%) with available electrocardiographic records, tachyarrhythmia was detected in 20 patients, sinus tachycardia was detected in six patients, right ventricular hypertrophy in nine patients, the atrioventricular block in two patients, Wolf Parkinson White (WPW) in one patient, and tachyarrhythmia in one patient. and frequent ventricular extrasystoles in one patient.

The highest pro-BNP levels were found in the sepsis group when the patients were divided into six groups: cardiac, respiratory, sepsis, nephrological, neurological, and hematological (Pro-BNP median levels QR 25-75: 355 pg/mL (62-3147), 375 pg/mL (69-3822), 1213 pg/mL (65-19386), 365 pg/mL (36-9644), 850 pg/mL (64-35000), and 104 pg/mL (29-1283), respectively). In comparison to the cardiac, nephrological, and hematological groups, the pro-BNP levels in the sepsis group were significantly higher (p= 0.03, 0.044, and 0.001, respectively). The hematological group's pro-BNP levels were significantly lower than those of the other groups' (p= 0.001, 0.001, 0.001, 0.019, and 0.015, respectively). The median troponin T levels in the cardiac group were 0.006 (0.004-0.019) ng/mL and in the respiratory group, they were 0.009 (0.005-0.048) ng/mL. The troponin T in the respiratory group were significantly higher than cardiac group (p= 0.018). In the sepsis group, the median troponin T levels were 0.008 (0.006- 0.088) ng/mL, while in the hematological group, it was 0.006 (0.004-0.011) ng/ml. The median troponin T in the sepsis group were significantly higher (p= 0.048) compared to the hematological group and significantly lower (p= 0.013) compared to the respiratory group. **Table 1** shows the correlations of the pro-BNP levels and other parameters.

Table 1. Correlation of Pro-BNP level with clinical and laboratory data

	Correlation Coefficient	p
Length of stay in hospital	0.496	<0.0001
Years	-0.512	<0.0001
Height	-0.531	<0.0001
Weight	-0.534	<0.0001
Troponin	0.568	<0.0001
C-reactive protein	0.164	<0.0001
Procalcitonin	0.550	<0.0001
Hemoglobin	-0.493	<0.0001
Hematocrit	-0.454	<0.0001
ALT	0.280	<0.0001
AST	0.388	<0.0001
Creatinine	-0.159	<0.0001
Albumin	-0.459	<0.0001
TR velocity	0.357	<0.0001
LVEDD z score	0.205	<0.0001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, TR:Tricuspit regurgitation, LVEDD: left ventricul end-diastolic diameter

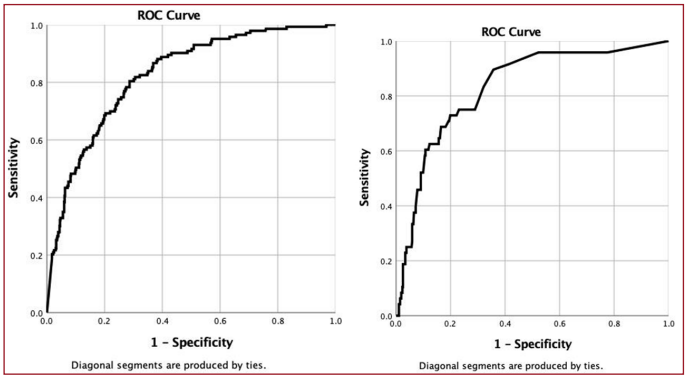
In the 143 patients who had one or more events had developed follow-up. Cardiac surgery was required in 71, interventional angiography in 8, tachyarrhythmia requiring ablation in one, uncontrolled congestive heart failure in one, arrhythmia in 4, and repeated hospitalizations in 12 patients. Among these 143 patients, 46 had died. In 13 cases, the second event had gone further. **Table 2** shows comparison of the data of the group with and without CVE.

The presence of fever and tachycardia did not show a significant correlation with the CVE, but tachypnea (p 0.0001 Exp(B): 0.106, B: -2.243, lower: 0.067, upper: 0.168) and blood culture positive (p< 0.0001 Exp(B): 0.171, B:–1.763, 95% CI lower:0.065, upper:0.451) had positive correlations. The pro-BNP level (p< 0.0001 Exp(B):1, B: 0.95% CI lower:1, upper:1), the LVEDD z score (p=0.008 Exp(B):0.837, B:–0.178, 95% CI lower:0.733, upper:0.955), and the TR velocity (p<0.0001 Exp(B):0.444, B:–0.812, 95% CI lower:0.305, upper:0.647) were revealed as the significant positive predictors of the CVE. In terms of the development of CVE, 84% sensitivity and 65% specificity were revealed when using 350pg/mL pro-BNP and Ross scoring for the ROC analysis, while 58% sensitivity and 85% specificity were revealed for 1701pg/mL Pro-BNP (13). When using troponin T at 0.0014ng/mL for event detection, 73% sensitivity and 79% specificity were revealed (**Graph 2A** and **2B**).

Table 2. Comparison of the data of the group with and without cardiovascular event

	With cardiovascular event	Without cardiovascular event	p
	Median (min- max)	Median(min-max)	
Ages (month)	9 (1-210)	95.5 (1-251)	<0.001
Height (cm)	66 (45-182)	124.0 (44-184)	<0.001
Weight (kg)	6.34 (1.32- 100)	25 (2.25-112)	<0.001
TR Velocity (m/s)	2.5 (1.1-5)	2 (1-5.4)	<0.001
LVEDD z score	1.4 (-3.02- 9.56)	0.42 (-2- 6.84)	<0.001
Peak Pro-BNP (pg/ml)	3013 (6.69- 35000)	144 (1.98- 35000)	<0.001
Troponin (ng/ml)	0.052 (0.003-1.56)	0.006 (0.003- 3.35)	<0.001
C- reactive protein (mg/L)	0.5 (0.001-119.8)	0.6 (0- 134.2)	
Procalcitonin (ng/ml)	0.378 (0.2-100)	0.1050 (0.0001-100)	<0.001
Hemoglobin (g/dl)	10.8 (5.7-19.9)	12.6 (5.7-19)	<0.001
Hematocrit (%)	32.7 (18- 64.6)	37 (14.4-52)	<0.001
ALT (IU/L)	23.5 (4-1207)	14 (2- 253)	<0.001
AST (IU/L)	40 (15- 5582)	27 (8- 337)	<0.001
Creatinine (mg/dl)	0.33 (0.04- 4.08)	0.44(0.05- 13.11)	<0.001
Albumin (g/dl)	3.9 (1.1- 5.2)	4.2 (0.53- 5.7)	<0.001
Sex (Female %)	46.9	48.2	0.762
Fever (%)	21.7	12.4	0.004
Tachypnea (%)	61.5	15.1	<0.001
Tachycardia (%)	47.6	14.3	<0.001
ECG pathology (%)	9.7	4.9	<0.001
Positive hemoculture (%)	12.7	2	<0.001
Angiography (%)	21.7	2	<0.001
Cardiomegaly (%)	48.3	5.8	<0.001
Length of stay in hospital (days)	7 (0-73)	0 (0-76)	<0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, TR:Tricuspit regurgitation, LVEDD: left ventricul end-diastolic diameter, ECG: electrocardiography



Graph 2 A: ROC analysis for cardiovascular event predictor of Pro BNP, **2B**: ROC analysis for troponin T predictive of cardiovascular events

DISCUSSION

In the present study, pro-BNP, LVEDD z score, and TR velocity were shown to be the most significant predictors for CVE. Pro-BNP levels were strongly correlated with patient age, height, and weight negatively, but troponin T and procalcitonin levels were strongly correlated positively. The sepsis group had the highest pro-BNP level. The patients with complex CHD, pulmonary hypertension, and cardiomyopathy in the cardiac group had the highest pro-BNP values. There is not much research in the literature that compares several diagnostic groups, similar to the present study. Kim et al.[10] divided into cardiac, infectious, non-cardiac, and non-infectious groups and assessed the levels of pro-BNP in each group. The pro-BNP value was significantly higher in the cardiac group, and there was a positive correlation between pro-BNP levels and the requirement for mechanical ventilation, oxygen treatment, inotrope use, changed mental status, and death. Contrarily, even though the total number of patients in each group was significantly larger in our study, the pro-BNP levels were not higher in the cardiac group than the others. However, the group with major CVE in our study had higher pro-BNP levels, and the regression analysis found to be an independent predictor for CVE. In addition, unlike the earlier study, the association between troponin T level and the pro-BNP levels was also examined in the present study, demonstrating a significant positive correlation. Pro-BNP elevation can also be seen in noncardiac diseases due to secondary cardiac effects. There is no consensus on the distinction, especially in the childhood age group, and it is given as a class 2b recommendation in the guidelines.

Sepsis is strongly correlated with pro-BNP levels, which are higher in severe sepsis. Additionally, it has been previously shown that an increase in pro-BNP levels is associated with left ventricular dysfunction, mechanical ventilation support, oxygen therapy, the need for inotropic therapy, and a change in mental status, but not with systemic inflammatory response syndrome or mortality.[12,14,15] Pro-BNP and procalcitonin levels

were shown to be strongly correlated in our research, as has been noted in the literature.[9] Additionally, the sepsis group had the highest levels of pro-BNP. This may be explained by the fact that the majority of these patients were treated in the critical care unit for their severe sepsis. The pro-BNP levels in the group with severe sepsis were high, which is consistent with the literature. The pro-BNP levels showed no association with mortality in the sepsis group, according to the literature.[12] While no mortality assessment was conducted for the sepsis group in our study, when the whole group was examined, the pro-BNP value was revealed as an independent positive predictor for CVE.

Pro-BNP levels were found to help separate the respiratory reasons from the cardiac causes in research involving 49 kids.[16] The levels of pro-BNP may also help identify cardiac disease from non-cardiac diseases, according to several research.[7,16-20] However, there was no difference between the respiratory group and the cardiac group's pro-BNP levels also found higher troponin T level in the current investigation. This may be due to the tendency to test pro-BNP levels in patients with more severe respiratory symptoms. At the same time, most of the patients in the cardiac group have hemodynamically significant congenital heart disease, however, no significant difference was found in our patient group. It may be associated with cardiac involvement secondary to hypoxia due to severe respiratory disease.

In an metaanalysis in which cardiotoxicity is evaluated in pediatric cancer patients, increased pro-BNP levels were shown to be correlated with the degree of left ventricular but it has been reported that the sensitivity was low and not predictive.[21] According to reports, although this value helps validate exclusions, there is no established pro-BNP value for assessing left ventricular dysfunction in cancer patients.[15] Although there were no cancer patients with substantial left ventricular dysfunction in our research, there was a favorable association between the pro-BNP and the hemoglobin and hematocrit levels. Additionally, the hematological group's significance of this correlation was discovered to be lower than that of the other groups, which might be explained by the lack of a patient with significant left ventricular failure.

Pro-BNP levels have been shown to rise in renal failure patients in correlation with the degree of kidney failure and the results of echocardiography, with a positive predictive value for cardiac strain.[22] The levels of pro-BNP and creatinine showed only a minor correlation in our study. However, in the case of volume overload leading to ventricular dilatation or an increase in the right ventricular pressure, positive predictive power in predicting the development of CVE was detected, in line with previous research.

In comparison to children with simple congenital heart diseases, children with complex congenital heart problems were shown to have greater levels of pro-BNP.[5,23] In similar to previous research, individuals with complex heart disease and cardiomyopathy had the highest levels of pro-BNP.[7] Patients with volume overload and systolic ventricular dysfunction in particular had higher levels of Pro BNP.[8] Pro-BNP levels were found to be higher in complex cyanotic patients, such as a single ventricle in our study. Other research with similar findings has shown that individuals with complex cardiac disease have greater BNP levels.[17,24,25] There is enough data to support the BNP level's utility in diagnosis and follow-up, although it has not yet been confirmed that it might serve as a sufficient diagnostic marker for pediatric pulmonary hypertension. In the present study as well, a significant increase in the BNP levels was observed in the group of patients with left-right shunt and inoperable pulmonary hypertension.

Additionally, compared to individuals with congenital heart disease, people with volume and pressure load had greater BNP values.[4] Consistent with this, in the present study, patients with pulmonary arterial hypertension and high LVEDD scores presented higher BNP levels. Additionally, a positive correlation between BNP levels and the TR velocity and LVEDD z-score was noted.

The New York Heart Association (NHYA) classification and the pro-BNP levels were found to be positively correlated by Sahin et al.[5] Ross classification-based relationships have not yet been the subject of any studies.[13] Although the NHYA or Ross classification could not be used in the current investigation since it was retrospective in nature, there was a strong association between the presence of tachypnea, tachycardia, and cardiomegaly.

The current study has some limitations, retrospective design, the non-homogeneous patient population. Additionally, some patient information, such as electrocardiography data were unavailable, and some patients' follow-up information was not available either because hospital staff failed to follow-up.

CONCLUSION

The development of CVE was shown to be independently related to the Pro-BNP level. In addition, the presence of tachypnea, the Pro-BNP level, the TR velocity, and the LVEDD z-score were the most significant predictors of CVE. Moreover, unlike the findings obtained for adults, the benefit of using the Pro-BNP levels for determining cardiac diseases in children could not be demonstrated in the present study. Therefore, it is advised that randomized prospective studies be carried out to show the value of Pro-BNP in separating cardiac disorders from non-cardiac diseases in children.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskisehir Osmangazi University non-interventional researches Ethics Committee (Decision No: 2020-181, 25403353-050.99-E.52038).

Informed Consent: The data were obtained retrospectively from electronic medical records.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Laryngeal Mask Airway Versus Endotracheal Intubation for Airway Management During Percutaneous Dilatational Tracheostomy

Perkütan Dilatasyon Trakeostomisi için Hava Yolu Yönetiminde Laringeal Maske ve Endotrakeal Entübasyonun Karşılaştırılması

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Abstract

Aim: Tracheostomy is a common procedure performed surgically or percutaneously due to prolonged intubation. During the procedure, airway safety can be ensured using a laryngeal mask airway (LMA) or an endotracheal tube (ETT). The aim of this study was to investigate the complications associated with the use of LMA and ETT during the tracheostomy procedure, operative time, and changes in blood gas parameters.

Material and Method: This study included patients admitted to the Intensive Care Units of Burdur State Hospital between 2019 and 2023. A total of 78 patients were divided into two groups: ETT (n=39) and LMA (n=39). Procedure-related complications, operative time, blood gas data were recorded from the patient files.

Results: There was no statistically significant difference between the LMA and ETT groups in terms of complications. There was also no statistically significant difference in postoperative values of PaCO2 between the groups (p<0.439). The analysis of pre- and post-tracheostomy PaO2 values indicated a decrease in both the LMA and ETT groups (p< 0.001 for both). The comparison of the two groups by the duration of the tracheostomy procedure showed a statistically significant shorter operative time in the LMA group than in the ETT group (p< 0.001).

Conclusion: Our study demonstrated no statistically significant difference between LMA and ETT in terms of complications and changes in blood gas parameters. Tracheostomy with LMA has advantages over ETT, fewer personnel requirements during the procedure, clear vision in bronchoscopy, and shorter operative time.

Keywords: Percutaneous dilatational tracheostomy, laryngeal mask airway, blood gas, complication

Öz

Amaç: Trakeostomi işlemi uzamış entübasyon nedeniyle cerrahi yada perkütan teknik kullanılarak yapılan bir işlemdir. Bu işlem sırasında hava yolu güvenliği laringeal maske (LMA) ya da endotrakeal tüp (ETT) ile sağlanmaktadır. Bu çalışmada trakeostomi işlemi esnasında LMA ve ETT kullanımının komplikasyonlarını, işlem süresini ve kan gazı verilerindeki değişimlerini incelmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 2019-2023 yılları arasında Burdur Devlet Hastanesi Yoğun Bakım Kliniklerinde yatan hastalar dahil edilmiştir. Çalışmaya dahil edilen 78 hasta; ETT (n=39) ve LMA (n=39) kullanılanlar olarak iki gruba ayrılmıştır. İşleme ait komplikasyonlar, işlem süreleri, hastaların kan gazı verileri hasta dosyalarından kaydedildi.

Bulgular: Gruplar arasında komplikasyonlar açısından istatistiksel fark bulunmadı. LMA ve ETT ile trakeostomi açılan gruplar arasında işlem sonrası PaCO2 değerlerinde istatiksel olarak anlamlı fark yoktu (p<0.439). Trakeostomi öncesi ve sonrası PaO2 değerleri değerlendirildiğinde, hem LMA ve hem de ETT gruplarında düşme olduğu görüldü (her ikisi için de) (p<0,001). Trakeostomi işlemi süreleri karşılaştırıldığında ise LMA grubunda sürenin ETT grubuna göre istatistiksel anlamlı olarak daha kısa olduğu görüldü (p<0,001).

Sonuç: Çalışmamızda komplikasyonlar ve kan gazında meydana gelen değişimler açısından LMA ve ETT arasında herhangi istatistiksel olarak bir fark olmadığı görülmüştür. LMA ile trakeostominin ETT ye göre işlem sırasında daha az personel ihtiyacı olması, bronkoskopide görüş netliği ve işlem süresinin daha kısa olması gibi avantajları vardır.

Anahtar Kelimeler: Perkütan dilatasyon trakeostomi, laringeal maske, kan gazı, komplikasyon

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INTRODUCTION

Tracheostomy is a procedure performed using either a surgical or percutaneous technique in cases of prolonged intubation. The key considerations in choosing tracheostomy include providing a safer airway, improving oral hygiene, facilitating nursing care, and increasing patient comfort.[1] Despite these benefits, there is still no consensus on the optimal timing for performing a tracheostomy. However, prolonged ventilation with endotracheal intubation brings about numerous complications.[2]

In recent years, the percutaneous tracheostomy technique has become the method of choice for tracheostomy in cases of prolonged intubation in intensive care units. The percutaneous dilatation technique has been associated with lower incidence of complications such as bleeding and wound infection compared to surgical tracheostomy. Moreover, percutaneous tracheostomy offers advantages such as lower mortality rates and easier bedside operation.[3]

One of the common challenges associated with the use of an endotracheal tube (ETT) during percutaneous tracheostomy is cuff rupture, and inadvertent perforation of the tracheal ring by the needle through Murphy's eye of ETT, which can result in needle movement along with the ETT and procedure failure.[4,5] To address these challenges, some centers have adopted the use of a laryngeal mask airway (LMA) during the percutaneous tracheostomy procedure in their clinical practice, due to issues associated with the endotracheal tube and prolonged tracheostomy procedures.[6] The use of LMA during the tracheostomy procedure aims to reduce the number of auxiliary personnel required and provide a better angle of view for bronchoscopy, without causing harm.[7]

This study aimed to assess the incidence of complications during and after the tracheostomy procedure using the percutaneous dilatation technique, and to compare the effectiveness of endotracheal intubation and laryngeal mask airway (LMA) in airway management during percutaneous dilatational tracheostomy (PDT).

MATERIALS AND METHODS

The study was carried out with the permission of Afyonkarahisar Health Sciences University Ethics Committee (Date: 07.04.2023, Decision No: 2023/226). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included patients aged 18 and above who were admitted to the Intensive Care Units of Burdur State Hospital between 2019 and 2023. Study data were obtained retrospectively by reviewing patient files. As part of our clinical practice, neck and airway ultrasound (US) is routinely performed for all patients undergoing tracheostomy to determine the tracheal ring where the tracheostomy needle will be inserted. Additionally, bronchoscopy is used throughout the procedure after establishing airway control with an endotracheal tube (ETT) or laryngeal mask airway (LMA).

Tracheostomy was performed using ETT in some patients and under the guidance of LMA in others. Patients were divided into two groups based on the airway management technique used during the tracheostomy procedure. Anesthetic drug doses, arterial blood gas data (including partial pressure of oxygen (PaO_2) and partial pressure of arterial carbon dioxide ($PaCO_2$), with the fraction of inspired oxygen (FiO_2) of 1 as 100% oxygen was used in the study), biochemical data, and information on mechanical ventilator settings were obtained from the patient records. Moreover, data on perioperative and postoperative complications were collected from standardized tracheostomy observation forms recorded in the patient files. The final sample size for analysis was 78 patients after excluding those with missing data, those who did not undergo bronchoscopy, those who underwent emergency tracheostomy, and those who died within 48 hours after tracheostomy. The flowchart of the study is shown in **Figure 1.**

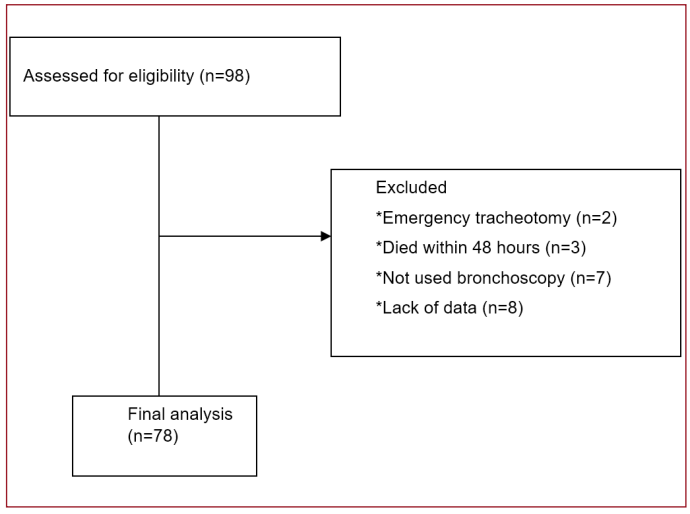

Figure 1. The flowchart of the study

Tracheostomy Procedure

The patients in both groups underwent a standard fasting period of 6 hours before the procedure, following the recommendations of the American Society of Anesthesiology (ASA).[8] Prior to each procedure, 100% oxygen was administered for 15 minutes. Sedation was achieved using propofol (100-200 µg/kg), while muscle relaxation was achieved using rocuronium (0.6 mg/kg).

Patients were placed in the supine position with the neck extended by a pillow placed under the shoulders. In the endotracheal tube (ETT) group, the cuff of the tracheal tube was retracted up to the vocal cords, while in the laryngeal mask airway (LMA) group, the endotracheal tube was removed and the LMA was placed. The neck region was cleansed with 10% povidone-iodine and covered with sterile drapes. Five mL of lidocaine 2% with adrenaline was subcutaneously administrated to the second and third

tracheal rings. A vertical incision of 1 cm in length was then made on the skin, and the trachea was visualized using a flexible bronchoscope through ETT or LMA. The needle location was confirmed by bronchoscopy. After advancing the wire through the needle, the tracheostomy cannula was inserted into the tracheal lumen. Bronchoscopy was used for guidance during the procedure. Once the location of the cannula was confirmed, the cuff was inflated.[9]

Statistical Analysis

Categorical variables were presented as percentages and frequencies. Normality of continuous variables was checked using the Shapiro-Wilk test. Normally distributed continuous variables were reported as mean ± standard deviation (SD), while non-normally distributed continuous variables were presented as median and interquartile range (IQR). The chi-square test was used to compare categorical variables between non-survivors and discharged patients, with Fisher's exact test applied when necessary. Independent-sample t-test was utilized to compare normally distributed continuous variables between the groups, while the Mann-Whitney U test was applied for non-normally distributed continuous variables. The paired t-test was used for comparisons of normally distributed variables at two time points, such as preoperative and postoperative $PaCO_2$ values. The Wilcoxon signed-rank testwas used for comparisons of non-normally distributed variables at two time points, including pre- and post-tracheostomy PaO_2.

RESULTS

Of the 78 patients included in the study, 60.3% (n=47) were male and 39.7% (n=31) were female. The median age of the study group was 70 years (IQR=20 years). During the intensive care follow-up, 61.5% (n=48) of our patients died, while 38.5% (n=30) were discharged. The demographic and clinical characteristics of patients who underwent tracheostomy with LMA (n=39) and ETT (n=39) are presented in **Table 1**. The operative time was statistically significantly shorter in the LMA group compared to the ETT group (p<0.001). Postoperative PaO_2 values were statistically significantly higher in the ETT group (p<0.001), while there was no statistically significant difference in postoperative $PaCO_2$ values.

Table 2 shows perioperative and postoperative complications of the tracheostomy procedure in patients who underwent tracheostomy using LMA and ETT.

There was a statistically significant increase in preoperative and postoperative $PaCO_2$ values of both the LMA and ETTgroups (p<0.001), as shown in **Table 3**.

As shown in **Table 4**, there was a statistically significant difference in preoperative and postoperative PaO_2/FiO_2 values of the groups that underwent tracheostomy with LMA and ETT.

Table 1: Demographic and clinical characteristics of patients who underwent tracheostomy with LMA and ETT

	LMA group (n=39)	ETT group (n=39)	p-value
Age (years), median (IQR)	68 (24)	72 (19)	0.097*
Gender			
Male	24 (51.1%)	23 (48.9%)	0.817**
Female	15 (48.4%)	16 (51.6%)	
Height (cm), median (IQR)	165 (10)	165 (10)	0.613*
Weight (kg), median (IQR)	70 (169)	72 (7)	0.110*
BMI, median (IQR)	24.6 (5.6)	26 (3.9)	0.028*
Diagnosis			
COPD	7 (41.2%)	10 (58.8%)	0.411*
Neurologicaldiseases	17 (56.7%)	13 (43.3%)	0.352*
Headtrauma	12 (42.9%)	16 (57.1%)	0.345*
Sepsis	3 (100%)	0	0.240*
SOFA score, median (IQR)	6 (3)	6 (1)	0.120*
APACHE-II score, median (IQR)	19 (8)	21 (6)	0.255*
Operative time (min)	4.52 (0.74)	6.39 (0.42)	<0.001*
Postoperative PaO_2 (IQR)	274 (63)	313 (29)	<0.001*
Postoperative $PaCO_2$ (mean±SD)	45.38±6.07	46.41±5.54	0.439***

*Mann-Whitney U test, **Fisher'sexact test, ***Student's t-test, LMA: Laryngeal Mask Airway; ETT: Endotracheal Tube, IQR: Interquartile range, BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, SOFA: The Sequential Organ Failure Assessment

Table 2: Complications of patients who underwent tracheostomy using LMA and ETT

	LMA group (n=39)	ETT group (n=39)
ETT cuffrupture	0	4 (10.3%)
Unplanned extubation	1 (2.6%)	0
Bleeding	1 (2.6%)	1 (2.6%)
Esophagealperforation	1 (2.6%)	0
Pneumothoraxemphysema	1 (2.6%)	0
Desaturation	1 (2.6%)	1 (2.6%)
Bronchospasm	1 (2.6%)	0
Increasein plateaupressure	1 (2.6%)	0
Pneumonia	5 (12.82%)	3 (7.69%)

LMA: Laryngeal Mask Airway, ETT: EndotrachealTube

Table 3: Pre- and post-tracheostomy blood gas $PaCO_2$ values of the LMA and ETT groups

	Preoperative $PaCO_2$ (mean±SD)	Postoperative $PaCO_2$ (mean±SD)	p-value
LMA group	40.15-4.77	45.38-6.07	<0.001*
ETT group	38.21-3.66	46.41-5.54	<0.001*

*Paired t-test, LMA: Laryngeal Mask Airway, ETT: Endotracheal Tube, SD: Standard Deviation

Table 4: Pre- and post-tracheostomy blood gas PaO_2/FiO_2 values of the LMA and ETT groups

	Preoperative PaO_2/FiO_2	Postoperative PaO_2/FiO_2	p-value
	Median(min-max)	Median (min-max)	
LMA group	328 (284-447)	274 (221-406)	<0.001*
ETT group	345 (282-449)	313 (270-421)	<0.001*

*Wilcoxon signed-rank test, LMA: Laryngeal Mask Airway, ETT: Endotracheal Tube

DISCUSSION

This study investigated the complications and operative times of LMA and ETT used for airway management during PDT procedures, as well as changes in respiratory mechanics and arterial blood gas parameters depending on the technique employed.

Respiratory failure often necessitates mechanical ventilation for critically ill patients in the intensive care unit. Either endotracheal intubation or tracheostomy is used for respiratory support. However, prolonged endotracheal intubation can lead to undesirable effects such as laryngeal injury, subglottic stenosis, increased sedation requirements, and difficulties in weaning from ventilatory support.[10]

During percutaneous tracheostomy, airway safety is established by utilizing either ETT or LMA, each with its own set of advantages and disadvantages. The PDT procedure performed with the assistance of endotracheal intubation can have various disadvantages, such as cuff rupture, puncture of the tube by needle, or inadvertent migration into Murphy's eye.[11]

Our study showed that various complications may develop during the PDT procedure. Airway and pulmonary complications were more frequently observed in the LMA group, although no statistically significant difference was found between the two groups in terms of complications. Cuff rupture was the most common complication in the ETT group, while pneumonia was the most frequent complication in the LMA group.

A large-scale study by Vargas et al. screening patients who underwent PDT reported that oxygen saturation decreased in 6.2% of the patients, indicating desaturation.[12] Our study demonstrated decreased oxygen saturation during the PDT procedure, with a desaturation rate of 2.56%. In the LMA group, there was 1 patient with bronchospasm and 1 patient with an increase in plateau pressure. We believe that this may be caused by secretions passing from the trachea to the bronchi and bronchioles, as the LMA used during the procedure is wider and does not settle on the epiglottis, thus not blocking the tracheal tract.

Yaghoubi et al. reported a rate of 5.7% for ETT cuff rupture during PDT,[13] while Araujo et al. reported a rate of 1.7% for ETT rupture.[14] In our study, we observed an endotracheal cuff rupture rate of 10.25%.

The incidence of bleeding, which is one of the early complications of tracheostomy, ranges from 0.6 to 5%.[15] Early bleeding is usually minor and not life-threatening, occurring within 48 hours and originating from superficial veins, and can be controlled with pressure. On the other hand, major bleedings result from tracheo-arterial fistula development during the procedure.[16] In our study, no major bleeding was observed after the PDT procedure, while the rate of minor bleeding was 2.56%. Bleeding was successfully controlled with pressure before proceeding with the procedure.

Pneumothorax and subcutaneous emphysema are also among the complications that may occur during the PDT procedure. Fikkers et al. reported a rate of 1.4% for subcutaneous emphysema and 0.8% for pneumothorax during PDT.[17] Kaiser et al. reported a rate of 2.08% for subcutaneous emphysema without tracheal wall damage.[18] In our study, subcutaneous emphysema was observed in only one patient in the LMA group (2.56%), which resolved within a few days without any respiratory complications. There were no cases of pneumothorax in both the LMA or ETT groups.

One of the rare but fatal late complications of the tracheostomy procedure is tracheo-esophageal fistula (TEF), which develops as a result of injury to the posterior tracheal wall. Epstein et al. reported that the incidence of this complication is below 1%.[19] A review by Goldenberg et al. reported that the rate of TEF after PDT was 0.08% and it was fatal.[20] In our study, TEF after PDT was observed only in the LMA group with a rate of 2.56%, and the case was managed through surgical intervention and returned to a normal course.

In a study comparing the effectiveness of LMA and ETT during the PDT procedure, Döşemeci et al. reported statistically significantly shorter operative time with LMA than with ETT.[21] Similarly, another study showed that the duration of PDT with LMA was shorter compared to ETT.[9] In our study, the duration of PDT with LMA was found to be statistically significantly shorter than with ETT. This may be considered as a reason to prefer LMA, as reduced operative time leads to decreased exposure to anesthetic drugs.

During the PDT procedure with ETT, the assistance of a second person is required to control the airway, specifically to pull the endotracheal tube up to the vocal cords. However, with LMA, there is no need for a second person to take control of the airway. Dexter et al. reported that the angle of view in bronchoscopy was better with LMA as it was located on the vocal cords, in contrast to ETT.[22] In our study, we also found that the use of LMA provided a better angle of view for the tracheal rings during the procedure, and the entry of the tracheostomy needle through the tracheal ring was visualized more clearly.

Previous studies have shown a statistically significant difference between pre- and post-PDT $PaCO_2$ values in both ETT and LMA, with postoperative $PaCO_2$ values being higher. Moreover, the increase between preoperative and postoperative measurements is greater with ETT. This has been attributed to the fact that bronchoscopy with ETT prolongs the operative time and is associated with airway leakage.[21,23,24]

In our study, postoperative $PaCO_2$ values were statistically significantly higher than preoperative values in both the ETT and LMA groups during the PDT procedure. However, the comparison of the ETT and LMA groups revealed no statistically significant difference in preoperative and postoperative $PaCO_2$ values.

Linstedt et al. reported a decrease in the PaO_2/FiO_2 ratio in both the LMA and ETT groups in their study comparing the use of LMA and ETT in the PDT procedure.[24] In our study, the comparison of preoperative and postoperative blood gas measurements also revealed a statistically significant decrease in PaO_2/FiO_2 values in both groups.

A study by Zhang et al. comparing surgical tracheostomy and PDT reported no statistically significant difference between the two groups in terms of ventilator-associated pneumonia (VAP).[25] Similarly, Terragni et al. reported a VAP rate of 8.3%.[26] In our study, the evaluation of bacterial growth of deep tracheal aspirate cultures, clinical findings, and the presence of pneumonia before and after the PDT procedure showed that 12.82% of patients in the LMA group and 7.69% of patients in the ETT group developed pneumonia. However, there was no statistically significant difference between the groups. We believe that the development of pneumonia is not solely related to the PDT procedure. Further prospective studies with larger sample sizes are needed to confirm these results.

Our study has some limitations that should be considered. The first limitation of our study is its retrospective and single-center design. The second limitation is the small number of patients.

CONCLUSION

Tracheostomy is a common procedure performed in intensive care units, particularly in cases of prolonged mechanical ventilation. The use of ultrasound (US) and flexible bronchoscopy (FOB) during the PDT procedure is considered a reliable and effective method for airway evaluation. Our study showed a decrease in pre- and post-tracheostomy PaO_2/FiO_2 values in both the LMA and ETT groups. Moreover, the duration of the tracheostomy procedure was found to be statistically significantly shorter in the LMA group compared to the ETT group. Based on our results, we believe that the use of LMA is preferable due to its shorter operative time, increased patient comfort, reduced personnel requirement, and improved clarity of vision during bronchoscopy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Afyonkarahisar Health Sciences University Ethics Committee (Date: 07.04.2023, Decision No: 2023/226).

Informed Consent: The data were obtained retrospectively from electronic medical records.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Comparison of Supine Position and Traction Table in Surgical Treatment of Unstable Intertrochanteric Fractures with PFNA

İnstabil İntertrokanterik Kırıkların PFNA ile Cerrahi Tedavisinde Supin Pozisyon ile Traksiyon Masasının Karşılaştırılması

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Abstract

Aim: Intertrochanteric femur fractures (IFF) are a major cause of morbidity and mortality in the elderly population. Proximal femoral nail-anti-rotation (PFNA) is one of the most preferred surgical treatment methods. This study aimed to compare the clinical and radiologic results of two different patient positions used during PFNA and to reveal the intraoperative advantages and disadvantages.

Material and Method: Cases operated due to IFF between January 2020 and December 2022 were retrospectively analyzed. The study was conducted with 123 patients meeting the inclusion criteria. The minimum follow-up period was determined as one year. Two groups were formed: those operated on the traction table (opereted-TT) and those operated in supine lithotomy without traction table (operated-SP). The groups were compared regarding operative time, reduction quality, type-apex distance (calTAD), and radiologic and clinical results.

Results: There were 76 patients in the operated-TT group and 47 in the operated-SP group. The mean age of the operated-TT group was 81.00±8.52 years, and the mean age of the operated-SP group was 79.30±8.12 years. (p=0.213) Gender, follow-up time, time from trauma to surgery, and fracture classification were similar for the groups. The mean operative time was 95.18±8.54 minutes in the operated-TT group and 88.23±7.12 minutes in the operated-SP group, and the operation was completed in a shorter time in the operated-SP group. (p=0.001) There were no differences between the groups in terms of reduction quality, calTAD, Harris Hip Score, VAS score, infection rates, and cut-out rates.

Conclusion: Based on this study, the radiologic and clinical results of the cases operated with manual traction in the supine position and those operated using a traction table in treating IFF with PFNA are similar. In addition, it was concluded that shorter operation time was an advantage of the operated-SP group.

Keywords: Intertrochanteric fracture, proximal femoral nail anti-rotation, position

Öz

Amaç: İntertrokanterik femur kırıkları (IFF) yaşlı popülasyonda önemli morbidite ve mortalite sebebidir. Cerrahi tedavisinde proksimal femoral nail-antirotation (PFNA) en sık tercih edilen yöntemlerden biridir. Çalışmanın amacı; PFNA uygulanırken kullanılan iki farklı hasta pozisyonunun klinik ve radyolojik sonuçlarını karşılaştırmak, intraoperatif avantaj ve dezavantajlarını ortaya çıkarmaktır.

Gereç ve Yöntem: Ocak 2020 ile Aralık 2022 yılları arasında IFF nedeni ile opere edilen olgular retrospektif olarak incelendi. Dahil edilme kriterlerine uyan 123 olgu ile çalışma yürütüldü. Minimum takip süresi bir yıl olarak belirlendi. Traksiyon masasında opere edilenler (opereted-TT) ile traksiyon masasız supin litotomi pozisyonda opere edilenler (opereted-SP) olarak iki grup oluşturuldu. Gruplar ameliyat süresi, redüksiyon kalitesi, type-apex distance (calTAD), radyolojik ve klinik sonuçlar açısından karşılaştırıldı.

Bulgular: Opereted-TT grubunda 76, opereted-SP grubunda 47 hasta yer aldı. Opereted-TT grubunun yaşı ortalama 81.00±8.52 yıl, opereted-SP grubunun yaşı ortalama 79.30±8.12 yıl idi. (p=0.213) Cinsiyet, takip süresi, travmadan ameliyata kadar geçen süre ve kırık sınıflaması gruplar için benzerdi. Ameliyat süresi opereted-TT grubunda ortalama 95.18±8.54 dakika, opereted-SP grubunda ortalama 88.23±7.12 dakika olarak tespit edildi ve opereted-SP grubunda ameliyatın daha kısa sürede tamamlandığı görüldü. (p=0.001) Reduction quality, calTAD, Harris Hip Score, VAS skoru, enfeksiyon oranları, cut-out oranları açısından gruplar arasında fark tespit edilmedi.

Sonuçlar: Bu çalışmaya göre; IFF'nin PFNA ile tedavisinde supin pozisyonda manuel traksiyon ile opere edilen olgular ile traksiyon masası kullanarak opere edilen olguların radyolojik ve klinik sonuçları benzerdir. Bunun yanında ameliyat süresinin daha kısa olmasının opereted-SP grubunun avantajı olduğu sonucuna ulaşılmıştır.

Anahtar Kelimeler: İntertrokanterik kırık, proksimal femoral çivi anti-rotasyon, pozisyon

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INTRODUCTION

The rate of intertrochanteric femur fractures (IFF) has increased with the aging population, especially in older individuals.[1] Surgical treatment allows patients to reach their functional capacity earlier. In this way, complications and mortality caused by prolonged bed rest are significantly reduced.[2] Although there are different implant options in surgical treatment, cephalomedullary nails are the most preferred method, especially in unstable fractures.[3] Today, proximal femoral nail-anti-rotation (PFNA) is the most commonly used intramedullary nail.[4] The most important complication after PFNA is implant-related mechanical complications requiring reoperation. The most important way to prevent this is to ensure a successful reduction and correct placement of the nail.[5] In addition to successful implant placement, the duration of surgery also has a significant effect on complications. Different surgical positions have been described for successful reduction and implant placement. The most commonly used ones are traction table, lateral position, and operating in the supine position.[6,7] Each position has advantages and disadvantages. Significant complications of the commonly used traction table have been described, including pudendal nerve palsy, sciatic nerve palsy, common peroneal nerve palsy, erectile dysfunction, soft tissue contusions, pressure sores, compartment syndrome, and vascular injuries.[8] The aim of this study was to compare the clinical and radiologic results of performing surgery with manual traction in the supine lithotomy position without a traction table versus the commonly used traction table in the surgical treatment of IFF with PFNA.

MATERIAL AND METHOD

Patient Selection

The study was carried out with the permission of Umraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 24.04.2023, Decision No: 136). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was obtained from the patients included in the study. Between January 2020 and December 2022, 396 patients treated for IFF were retrospectively analyzed. Fracture classification was made according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association classification (AO/OTA). Patients who were operated on using short proximal femoral nail-anti-rotation (PFNA), aged 65 years or older, with a follow-up period of more than one year, and fracture types A2.2, A2.3 and A3 as per AO classification were included in the study. Patients treated conservatively, operated using a method other than PFNA, operated using a long nail, required open reduction, did not comply with follow-up, had a follow-up period of less than one year, underwent general anesthesia, previously operated on the same extremity, had a pathological fracture, and were A1 and A2.1 according to the AO classification were excluded from the study. Two groups were formed: those operated with manual traction in a supine lithotomy position without a traction table (operated-SP) and those operated with a traction table (operated-TT).

Surgical technique

All patients included in the study were operated on under spinal anesthesia. Two different surgeons performed the operations. The surgeon preferred the choice of patient position. In the Operated-TT group, the patients were placed on the traction table after anesthesia without any reduction maneuver. Internal rotation, adduction, and traction were applied. The reduction was checked on anteroposterior and lateral radiographs by fluoroscopy. In Opereted-SP, the intact extremity was suspended with a leg sling with the hip and knee flexed. In this way, it was aimed to obtain an accurate lateral radiograph. Internal rotation, adduction, and traction were applied with the help of an assistant throughout the operation. The reduction was checked on anteroposterior and lateral radiographs with fluoroscopy. The same incision and surgical technique were used in both groups. An incision was made proximal to the trochanter major, then a short PFNA with a trochanteric groove was inserted (TST-PROFIN-Proximal Femur Nail, 9-11) millimeters (mm) in diameter, 170-220 mm in length). Two proximal screws and one distal locking screw were placed, and the operation was finalized.

Postoperative Follow-up

Standard physical therapy protocol was applied to all patients postoperatively. They were instructed to perform quadriceps, ankle dorsiflexion, and knee and hip stretching exercises in the early period. On the first or second postoperative day, all patients were ambulated without any load on the operated extremity. Radiographs were taken on the first postoperative day, the first, third, sixth month, and one year postoperatively. X-ray control during the first postoperative month was awaited for weight-bearing instruction.

Clinical and Radiological Evaluation

AO classification was used for fracture classification. Demographic data, side of the injured extremity, fracture mechanism, time from fracture to surgery, and duration of surgery were analyzed. Surgery duration was considered the time from the completion of anesthesia to wound closure. The results were determined from the operating room records and analyzed. The reduction quality, type apex distance (calTAD), union time, and union problems were compared radiologically. Reduction quality was measured on anteroposterior and lateral radiographs taken on the first postoperative day as described by Chang et al.[9] and recorded as good, fair, and poor. calTAD was measured on radiographs taken on the first postoperative day and on nails with double proximal screw design as described by Buyukdogan et al.[10] Clinically, Harris Hip Score (HHS) and VAS scores were compared between the groups. Clinical scores were obtained from the first-year follow-up data.

Statistical analysis

SPSS 22.0 for the Windows program was used for statistical analysis. Descriptive statistics were expressed as numbers and percentages for categorical variables and mean, standard deviation, minimum, and maximum for numerical variables. Two independent groups were compared with Student's t-test when numerical variables met the normal distribution condition and with the Mann-Whitney U test when they did not. Rates in independent groups were compared using the Chi-Square Test. The statistical significance level was accepted as $p<0.05$.

RESULTS

The study was conducted with 123 patients fulfilling the inclusion criteria. There were 76 patients in the operated-TT group and 47 in the operated-SP group. The mean age of the operated-TT group was 81.00±8.52 years, while the mean age of the operated-SP group was 79.30±8.12 years. (p=0.213) There were 51 females and 25 males in the operated-TT group and 29 females and 18 males in the operated-SP group. (p=0.540) The time from trauma to surgery and AO classification were similar for the groups. The mean follow-up time was 19.68±3.90 months in the operated-TT group and 20.45±3.98 months in the operated-SP group. (p=0.262) (**Table 1**) The mean operative time was 95.18±8.54 minutes in the operated-TT group and 88.23±7.12 minutes in the operated-SP group, and the operation was completed in a shorter time in the operated-SP group. (p=0.001) There was no difference between the groups regarding reduction quality, calTAD, HHS, and VAS scores. Superficial infection was detected in four patients in the operated-TT group and two patients in the operated-SP group. (p=0.800) After oral antibiotic treatment, the infection resolved spontaneously without requiring additional surgical intervention. Cut-out occurred in four cases in the operated-TT group and three cases in the operated-SP group (p=0.790). Revision surgery was performed by removing the PFNA and applying hemiarthroplasty. No additional intervention was required in these four cases. (**Table 2**)

Table 1. Descriptive statistics and comparison results for demographic and general characteristics of the groups.

	Group		p
	SP (n=47)	TT (n=76)	
Gender (n,%)			0.540
Male	18 (38.30)	25 (32.89)	
Female	29 (61.70)	51 (67.11)	
Age(years)(mean±sd)	79.30±8.12	81.00±8.52	0.213
Follow up (Month) (mean±sd)	20.45±3.98	19.68±3.90	0.262
Surgical time (minute) (mean±sd)	88.23±7.12	95.18±8.54	0.001
AO Type (n,%)			0.900
A2.2	17 (36.17)	25 (32.89)	
A2.3	12 (25.53)	22 (28.95)	
A3	18 (38.30)	29 (38.16)	

sd:standard deviation

Table 2. Descriptive statistics and comparison results of radiological and clinical measurements of the groups

	Group		p
	SP (n=47)	TT (n=76)	
calTAD (milimeter) (mean±sd)	23.83±2.08	24.22±2.00	0.096
Reduction Quality (n,%)			0.780
Succesfull	26 (55.32)	46 (60.53)	
Moderate	19 (40.43)	26 (34.21)	
Poor	2 (4.26)	4 (5.26)	
Cut-out (n,%)	3 (6.38)	4 (5.26)	0.790
VAS score (mean±sd)	3.06±2.25	2.67±1.64	0.320
Harris Hip Score (mean±sd)	81.66±8.24	84.07±7.10	0.229
Superficial Infection (n,%)	2 (4.26)	4 (5.26)	0.800

calTAD:calculated tip apex distance, VAS: visual analugue scale, sd:standard deviation

DISCUSSION

IFF most commonly affects the elderly population. The morbidity and mortality that may occur due to this population's high number of comorbidities are alarming.[11] One of the main goals in treating IFF is to operate as soon as possible and mobilize the patient as quickly as possible. PFNA is considered an advantageous method in treating intertrochanteric femur fracture because it requires the shortest operation time and the least blood loss compared to other implant options.[12] Nevertheless, the search for obtaining more successful clinical and radiological results with PFNA, shortening the operation time, reducing blood loss, and obtaining a more stable fixation is still ongoing. The surgical position is one of these searches. Each position has its own advantages and disadvantages.

There are studies reporting that the stress exposure of soft tissues increases with prolonged surgical time, and the risk of surgical site infection increases with a decreased systemic defense of the organism.[13-15] As the surgical time increases, the amount of stress to which soft tissues are exposed increases, the systemic defense of the organism decreases, and the error rate increases due to fatigue in the team.[16,17] Since patients with intertrochanteric fractures are mostly elderly and have more comorbidities, it is inevitable that infection and surgical risks increase with prolonged operation time.[18] In one of the studies aimed at decreasing the operation time, Celik et al.[19] suggested the use of dual scopes in the treatment of intertrochanteric femur fractures with PFNA by using a fixed scope for anteroposterior radiography and a fixed scope for lateral radiography. They reported that this resulted in a significant reduction in operative time. Du et al.[20] compared PFNA cases operated with manual traction in the supine position with IFF cases operated with PFNA using a traction table and reported that the operation time was shorter in supine positions. In addition, they found similar clinical and radiologic results. In our study, the operative time was shorter in the operated-SP group compared to the operated-TT group. The short operative time is the most important advantage of the operated-SP group in treating intertrochanteric fractures with PFNA. In our study, the

preparation time after anesthesia, until the incision was made, was not evaluated separately, and the time from anesthesia to wound closure was considered the operative time. The reason for the shorter operation time in the Operated-SP group is thought to be the faster preparation phase.

Intraoperative blood loss is known to increase mortality and morbidity.[21,22] Yang et al.[23] reported that intraoperative blood loss in treating intertrochanteric fractures with PFNA might be higher than estimated. They emphasized that increased blood loss is associated with longer hospital stays and complications. In this study, there was no difference in the amount of intraoperative bleeding between the groups in treating intertrochanteric femur fractures with PFNA when the supine position or traction table operations were compared. One of the shortcomings of our study is that the amount of bleeding was not measured. We did not find any study showing a direct relationship between the duration of surgery and the amount of bleeding in treating intertrochanteric femur fractures with PFNA. Considering that the reason for the short operative time is due to the pre-incision preparation phase, it is understandable that the position preference is not directly related to the amount of bleeding.

The most important success indicator in the surgical treatment of intertrochanteric fractures with PFNA is the quality of reduction and correct positioning of the implant. Many open or closed techniques have been described to improve the quality of reduction.[24] In addition, the type-apex distance measured after placement of the proximal screws, as described by Baumgaertner et al.[25] increases the probability of implant success. In addition, the position of the proximal screws and the quality of the reduction are also important parameters that determine the success of the treatment.[26] In one of the studies investigating position selection and quality of reduction, Sahin et al.[7] compared patients operated on in a supine lithotomy position without a traction table with patients operated on using a traction table. They found a poor reduction in 2.9% of 30 patients operated in a supine position with manual traction and 6.7% of 34 patients operated with a traction table and found no difference between the groups in terms of reduction quality. They also found similar clinical results between the groups. Our study included only patients undergoing closed reduction. We aimed to evaluate the adequacy of two different positions in achieving a reduction in closed cases. Accordingly, poor reduction was observed in 4% of operated-SP cases and 5% of operated-TT cases. The reduction quality was similar for the groups. In addition, the fact that there was no difference between the groups in terms of calTAD, another important radiologic parameter, is an important indicator suggesting that the preference for supine position does not increase the possibility of poor reduction and implant failure.

This study has several limitations, including its retrospective design. Additionally, other significant limitations include the lack of evaluation of intraoperative bleeding and fluoroscopy amounts. Furthermore, the failure to separately evaluate the preparation time from the completion of anesthesia until the incision was made in measuring operative time can also be considered a limitation.

CONCLUSION

There are ongoing efforts to improve clinical and radiologic results, reduce complications, and improve perioperative surgery in the treatment of intertrochanteric femoral fractures with PFNA. In the study in which we compared the cases we operated with manual traction in the supine position without a traction table and the IFF cases we operated with a traction table, we concluded that although the radiologic and clinical results were similar between the groups, the advantage of the operated-SP group was the shorter operation time.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Umraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 24.04.2023, Decision No: 136).

Informed Consent: The data were obtained retrospectively from electronic medical records.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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