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A Quasi-Experimental Controlled Educational Intervention for Mothers to Reduce Unnecessary Emergency Department Admissions in Children with Respiratory Tract Infection Symptoms

ABSTRACT

Objective: Although children presenting with respiratory tract infection (RTI) symptoms can be managed by in primary care, these symptoms are the most common reasons for children to present to the emergency department (ED). The aim of this study is to investigate the effect of the education given to mothers by their family physician in reducing the unnecessary admissions of children with RTI symptoms to the ED.

Methods: This study was a quasi-experimental, single-blind, controlled educational intervention conducted with mothers of children aged 6 months-6 years. Family Medicine Units were randomized as control and intervention group. A questionnaire including sociodemographic characteristics, emergency department visits due to RTI symptoms, fever-related practices and knowledge, attitudes and behaviours (KAB) about RTI symptoms (KABaRTIS) was applied to both groups before and after the intervention. Intervention group received one-to-one, face-to-face education focusing on management of acute RTI symptoms and alarm findings, also a booklet was given. No intervention was made to the control group.

Results: Study was completed with 178 mothers (Control:118, Intervention:60). The KABaRTIS scores of the mothers increased significantly in both groups. The median number of admissions to ED due to RTI symptoms decreased for both groups. However, ED admissions due to severity increased in control-group and decreased in intervention-group.

Conclusions: This is the first educational intervention conducted in primary care in Türkiye to reduce unnecessary emergency department admissions with RTI symptoms in children. Nevertheless, population characteristics, interventional properties, contamination bias may have reduced the expected effect.

Keywords: Emergency Medical Services, Family Practice, Health Services Misuse, Respiratory Tract Infections.

Solunum Yolu Enfeksiyonu Belirtileri Gösteren Çocuklarda Gereksiz Acil Servis Başvurularını Azaltmak İçin Annelere Yönelik Yarı Deneysel Kontrollü Bir Eğitim Müdahalesi

ÖZET

Amaç: Solunum yolu enfeksiyonu (SYE) semptomları ile başvuran çocuklar birinci basamakta tedavi edilebilmesine rağmen, bu semptomlar çocukların acil servise başvurmalarının en yaygın nedenidir. Bu çalışmanın amacı, annelere aile hekimleri tarafından verilen eğitimin, SYE semptomları olan çocukların acil servise gereksiz başvurularını azaltma ve SYE hakkındaki bilgi, tutum ve davranışların geliştirilmesine etkisini araştırmaktır.

Gereç ve Yöntem: Çalışma, yarı deneysel, tek kör, kontrollü bir eğitim müdahalesi olup 6 ay-6 yaş arası çocukların anneleri ile yürütülmüştür. Aile Hekimliği birimleri kontrol ve müdahale grubu olarak randomize edilmiştir. Sosyodemografik özellikler, SYE semptomları nedeniyle acil servise başvurular, ateşle ilgili uygulamalar ve SYE semptomları hakkında bilgi, tutum ve davranış (BTD) önermelerini içeren anket, müdahale öncesi ve sonrasında her iki gruba da uygulanmıştır. Müdahale grubuna akut SYE semptomlarının ve alarm bulgularının yönetimine odaklanan bire bir, yüz yüze eğitim ve bir broşür verilmiştir. Kontrol grubuna herhangi bir müdahalede bulunulmamıştır.

Bulgular: Çalışma 178 anne ile tamamlanmıştır (Kontrol: 118, Müdahale: 60). Annelerin BTD puanları her iki grupta da anlamlı olarak artmıştır. SYE semptomları nedeniyle acil servise yapılan başvuruların ortanca sayısı her iki grup için de azalmıştır. Ancak, hastalık şiddeti nedeniyle acil servise başvurular kontrol grubunda artarken müdahale grubunda azalmıştır.

Sonuç: Bu çalışma, çocuklarda SYE semptomları ile gereksiz acil servis başvurularını azaltmak için Türkiye'de birinci basamakta yürütülen eğitim müdahalelerinin ilkidir. Bununla birlikte, popülasyon ve müdahale özellikleri, hatırlama ve bulaşma yanlılığı beklenen etkiyi azaltmış olabilir.

Anahtar Kelimeler: Acil Tıbbi Servisler, Aile Hekimliği, Sağlık Hizmetleri Suistimali, Solunum Yolu Enfeksiyonları.

INTRODUCTION

Admissions to emergency department (ED) in Türkiye constitute 28% of the use of health services, and the annual number of admissions to the ED is higher than the population of the country (1). 'Inappropriate', 'Non-urgent' or 'Unnecessary' admissions to the ED are complaints that do not require ED resources and immediate management (2). Patients use the ED to receive faster access to care without appointment, and for situations that could easily be resolved in Family Health Centers (FHC) (3). There are many studies on the reasons for admissions to the ED, its frequency, and the sociodemographic characteristics of the admissions. Acute upper respiratory tract infections (RTI) are the most common cause of admission to the pediatric ED in Türkiye. According to Türkiye Health Survey 2022 data, among the main health problems seen in the last 6-months in children aged 0-6, upper RTI ranks first with 31.3%, and RTI constitute almost half of all admissions in total (4). In some studies, it is reported that RTI constitute more than 50% of emergency admissions (3,5).

Especially in terms of protecting the health of 0–6-year-old children and fighting against diseases, mothers are in an important position. Factors like low socioeconomic level and low health literacy have been determined to increase the frequency of admissions to the pediatric ED (6). The fact that non-emergency admissions cause overcrowding in the ED, causes patients to wait longer, increases in health costs, low efficiency in emergency personnel, and low service quality (7). ED overcrowding is not a problem limited only to Türkiye. In the United States, Italy, Belgium, and many other countries, approximately half of pediatric emergency visits are non-urgent (8-10). Policies are being developed to solve this problem all over the world. Health education to parents about respiratory tract infection symptoms (RTIS) can make an important contribution to health promotion and resource management. Although there are studies examining the causes of this problem in Türkiye, no similar educational intervention study was found when the Turkish Medicine Index was scanned. However, there are examples of intervention from other countries (11,12).

Family medicine (FM) keeps the gate by providing preventive health services to patients and healthy individuals with a continuous and comprehensive approach and offers person-centered care to empower patients (13). It has been found that in health systems with a strong FM system, unnecessary admissions to the ED are less frequent (12). Family physicians (FP) can play a key role in improving the knowledge, attitudes, and behaviors (KAB) of mothers with healthy child follow-ups and the environment of trust between the physician and the patient. Therefore, a controlled educational intervention for mothers was aimed in a Family Health Center to reduce unnecessary emergency admissions in children with respiratory tract infection symptoms.

MATERIAL AND METHODS

Study Design: The research is a quasi-experimental, single-blinded, controlled educational intervention study. It was carried out at an Educational Family Health Center in İstanbul, Türkiye. The population of the study consists of all mothers with children aged 6-months to 6-years (6m-6y) who are registered to a specific Family Medicine Unit. The sampling of the study is shown in Figure 1.

It is estimated that the frequency of ED admissions will decrease by 50% in the intervention group, the minimum number required was found to be 58 for both the intervention and control groups. It was decided to reach at least 191 mothers (64:127) to increase the power of the analysis and assuming that 10% loss may occur until the completion of the study.

One of the 3-units of the FHC was assigned to the researcher by simple random method to form the intervention group and the other 2-units were accepted as the control group. All mothers who came to the FHC between the specified dates, met the criteria and agreed to participate in the study were included.

Inclusion Criteria in the Study:

• Having at least one child older than 6 months and younger than 6 years old

• No serious or chronic disease in that child (6m-6y).

Exclusion Criteria from the Study:

• Being a healthcare worker

• Serious illness diagnosis in the participant's child during the study

Data Collection

1. Initial Assessment: The participants were asked questions about their sociodemographic features and knowledge, attitude, and behavior (KAB) related to the management of RTIS. KAB was evaluated by a 5-point likert scale (1-"strongly disagree", 5-"strongly agree"), using a 20-sentence proposition formed by examining national and international sources on child health and diseases. Some sentences of the scale (1,2,5,9,14,16,19,20) were coded in reverse. A high score indicates expected positive knowledge, attitude, and behavior. The comprehensibility of the questions and Likert-type items was confirmed by a pilot study of the evaluation form. Educational status regarding childcare, the health institutions preferred, reasons for the preference, approach to the child with fever at home, and the number and the reasons to go to the ED or FHC or outpatient clinics in the last 6-months of the mothers were asked open-ended.

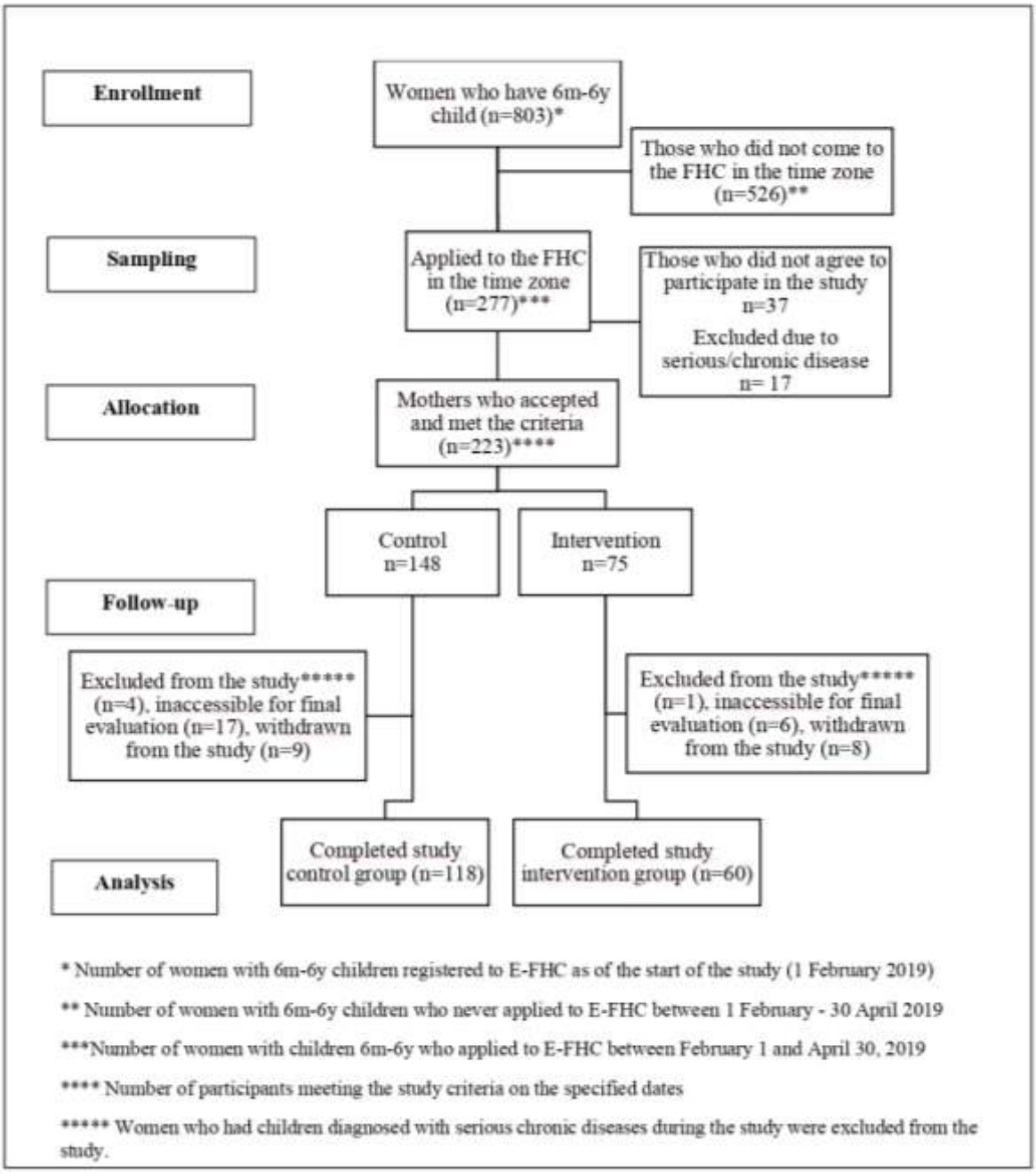

Figure 1. Flow diagram of sample selection process

2. Intervention: Individual Training: After the initial assessment, the intervention group mothers were given a face-to-face, one-on-one, approximately 15-minute standardized training on home management of acute respiratory tract symptoms and alarm findings were stated. A checklist was used for the standardization of education. Also, a leaflet and brochure prepared according to the guidelines were used as educational material (14-17). A pilot study was conducted for the brochure, and it was edited according to the feedback. No intervention was made to the mothers in the control group, and they were not informed about the intervention. The risk of contamination was reduced by training the intervention group in privacy, participants did not know which group they were in, and the final data collected by a blind researcher.

3. Final Evaluation: Six months after the educational intervention; all mothers participating in the study were invited to the FHC by phone by another researcher who was blind to the intervention and did not know which group the participants were in, and the same questionnaire were asked to the same mothers. At no stage of this study were the mothers informed of which group they were in. Thus, the research data was collected single-blind, and the participants were also kept half-blind.

Analysis Methods: The quantitative data of the study were analyzed with SPSS Statistics version 25. Number, percentage, mean, standard

deviation (StD), median, inter quantile range (iqr), minimum (min) and maximum (max) values were used. The assumption of normality of the data was confirmed by Kolmogorov Smirnov and Shapiro-Wilk tests. Independent t-test and paired t-test was used for normally distributed continuous variables, and also Mann-Whitney U test, McNemar test and Wilcoxon test were used for non-normally distributed variables. All open-ended questions were coded by two researchers, combined, categorized, and analyzed with the Chi-square test. Cronbach's alpha, the internal consistency coefficient of the KAB scale in our sample, was 0.68-0.72. Chi-square test and Fisher's exact test were used in the comparison of nominal data. Statistical significance was determined by taking the significance level of <0.05 and the power level of 80% in all analyzes.

Ethics: The study was conducted according to the guidelines laid down in the Declaration of Helsinki. The privacy rights of the participants were and will be always observed. Approval for the study was obtained from the Ethics Committee of Marmara University Faculty of Medicine with the protocol code of 09.2019.037 in 04.01.2019. Also, The Universal Trial Number (UTN) is U1111-1282-0650.

RESULTS

Sociodemographic Characteristics of the Participants: The study was completed with 178 mothers (Control:118, Intervention:60). The sociodemographic characteristics of the mothers were shown in Table 1. There was no difference in terms of sociodemographic characteristics of the participants except the number of mothers with 2-child was higher in the control group.

Table 1. Sociodemographic characteristics of the participants (n=178)

	Control [n=118 (%)]	Intervention [n=60 (%)]	P value*
Age (mean – StD)	32.9±4.7	32.4±4.8	0.481**
Age (min-max)	23-45	24-44	
Number of children [mean – (Std)]	2.10±0.93	1.78±0.80	**0.030****
Number of children [median – (iqr)]	2 (1-3)	2 (1-3)	**0.034*****
Number of children (min-max)	1-5	1-4	
Educational level (last finished)			0.876
Illiterate	1 (0.8)	0 (0.0)	
Primary School	17 (14.4)	10 (16.7)	
Middle School	12 (10.2)	4 (6.7)	
High School	34 (28.8)	18 (30.0)	
University and above	54 (45.8)	28 (46.7)	
Monthly household income			0.513
0-1600	5 (4.2)	1 (1.7)	
1601-5000	79 (66.9)	40 (67.8)	
5001 and above	34 (28.6)	18 (30.5)	
Employment status			0.258
Employed	97 (82.2)	45 (75.0)	
Unemployed - Housewife	21 (17.8)	15 (25.0)	
Marital status			1.000
Married	118 (100.0)	60 (100.0)	
Single	0 (0.0)	0 (0.0)	

**Chi-square test **Independent sample's t-test ***Mann Whitney - U*

The most preferred institution by the mothers for their children in case of RTIS was "Family Health Centers", the most preferred reason was "closeness" and there was no difference between the two groups (p=0.736). Also, there was no difference between the two groups in the reasons for applying to the ED (p=0.352).

Initial Assessment (Before): There was no significant difference between the groups in the reasons for admission to FHC or outpatient clinics, which were collected in 8-categories (RTIS, healthy child follow-up, fever, vaccination, acute gastroenteritis symptoms (AGES), allergy, rash-redness, and other) in the initial assessment (p=0.882). There was no significant difference between the groups in the reasons of admission to ED, which were grouped in 6-categories: fever, RTIS, AGES, rash-redness, trauma and other (p=0.717) at the beginning.

The practices of mothers in case of fever of their 6m-6y children were asked open-ended and were analyzed for coding. They were similar in both groups and there was no significant difference (p>0.05), while antipyretic drug administration was significantly more common in the intervention group (p=0.003).

The responses of the mothers to the scale consisting of 20-sentence Likert-type propositions were evaluated, and the Cronbach alpha coefficient, which shows the internal consistency before the intervention, was calculated as 0.679.

Final Evaluation (After): The preferred healthcare institution for their children was found to be FHC most frequently for both groups after the intervention (69.1%). Moreover, this preference increased significantly for both groups compared to the initial assessment (p<0.001). It was observed that the causes remained similar in the intervention

group but changed in the control group (C: p=<0.001; I: p=0.087).

In the final evaluation, when the factors affecting the child's admission to the ED for any health problem were asked, "24-hour care" (18.0%) was the most common, as in the initial assessment. The reasons for admission to the ED changed for both groups (p<0.001). However, while the number of people who stated that they went to the ED due to the severity of the disease decreased in the intervention group, it increased in the control group. It was observed that both groups preferred the ED less after the intervention, and the rate of decrease was greater in the intervention group (Table 2).

Table 2. Healthcare provider preferences for children of mothers in both groups before and after the intervention

	Intervention (n=60)			**Control (n=118)**			
	Before n (%)	**After n (%)**	**P value***	**Before n (%)**	**After n (%)**	**P value***	**Between Groups P value**
FHC	31 (51.7)	45 (75.0)		62 (52.5)	78 (66.1)		****=0.983**
ED	**15 (25.0)**	**5 (8.3)**	**<0.001**	**28 (23.7)**	**15 (12.7)**	**<0.001**	*****0.461**
Other	14 (23.3)	10 (16.7)		28 (23.7)	25 (21.2)		

* Comparison of family health center, emergency department and other health services, before and after the intervention (Chi-square test)
** Initial Assessment comparison of the groups (Chi -square test)
***: Final Evaluation comparison of the groups (Chi -square test)

Mothers applied less to FHC, or outpatient clinics compared to the initial assessment; it was observed that when they received care, they mostly went for RTIS and fever. There was a significant difference between the groups before and after the intervention (p<0.001), and there was no difference between the two groups (Table 3).

While there was a significant difference in the number of health services received from ED or FHC and outpatient clinics between the first and final evaluation in both the intervention and control groups, there was no significant difference between the intervention and control groups. The number of admissions per child is given in Table 3.

Table 3. Emergency department versus family health center or outpatient clinics admissions– before and after in intervention and control groups

	Intervention (n=60)			**Control (n=118)**			**Between groups P value**
	Before n (%)	**After n (%)**	**p value***	**Before n (%)**	**After n (%)**	**p value***	
FHC and Outpatient Clinics Admissions							
Mean (±SD)	4.52(±0.62)	2.72 (±0.32)		4.10 (±0.33)	2.76 (±0.22)		******=0.917
Median (IQR)	3 (IQR:3)	2 (IQR:2)	**=0.012**	3 (IQR:4)	2 (IQR:2)	**<0.001**	*******=0.669
Min-Max	0-30	0-11		0-23	0-15		
Emergency Department Admissions							
Mean (±SD)	1.00(±0.16)	0.92 (±0.17)		1.30 (±0.16)	0.69 (±0.10)		******=0.669
Median (IQR)	1 (IQR:1)	0.50(IQR:1)	=0.676	1 (IQR:2)	0.00 (IQR:1)	**<0.001**	*******=0.180
Min-Max	0-8	0-6		0-6	0-7		

* Comparison of the group, before and after intervention (*Wilcoxon* test)
** Initial Assessment comparison of both groups (*Mann-Whitney U* test)
***: Final Evaluation comparison of both groups (*Mann-Whitney U* test test)

Reasons for admission were collected in 3-categories (no admission, RTIS and other). Table 4 shows the data comparing the reasons for the intervention and control groups to go to ED or FHC and outpatient clinics in the initial assessment and final evaluation. While applying to the ED due to the severity of the disease increased in the control group, it is decreased in the intervention group. The other reasons are given in Figure 2.

Table 4. Comparison of the reasons for admission to emergency department or family health center and outpatient clinics in both groups before and after the intervention

	Intervention (n=60)			**Control (n=118)**			**Before ** After *** P value**
	Before n (%)	**After n (%)**	**p value***	**Before n (%)**	**After n (%)**	**p value***	
FHC and Outpatient Clinics Admissions							
No admission	2 (%3.3)	8 (%13.3)		7 (%5.9)	16 (%13.6)		******: =0.420
RTI Symptoms	44 (%73.4)	45 (%75.0)	0.615	86 (%72.9)	84 (%69.5)	0.348	*******:=0.771
Other	14 (%23.3)	7 (%11.7)		25 (%21.2)	20 (%16.9)		
Emergency Department Admissions							
No admission	25 (%41.7)	30 (%50.0)		52 (%44.1)	71 (%60.2)		******: =0.714
RTI Symptoms	27 (%45.0)	22 (%36.7)	0.492	55 (%46.6)	33 (%28.0)	**0.014***	*******:=0.413
Other	8 (%13.3)	8 (%13.3)		11 (%9.3)	14 (%11.9)		

* Comparison of groups before and after intervention (Chi-square test)
** Initial Assessment comparison of both groups (Chi -square test)
***: Final Evaluation comparison of both groups (Chi -square test)

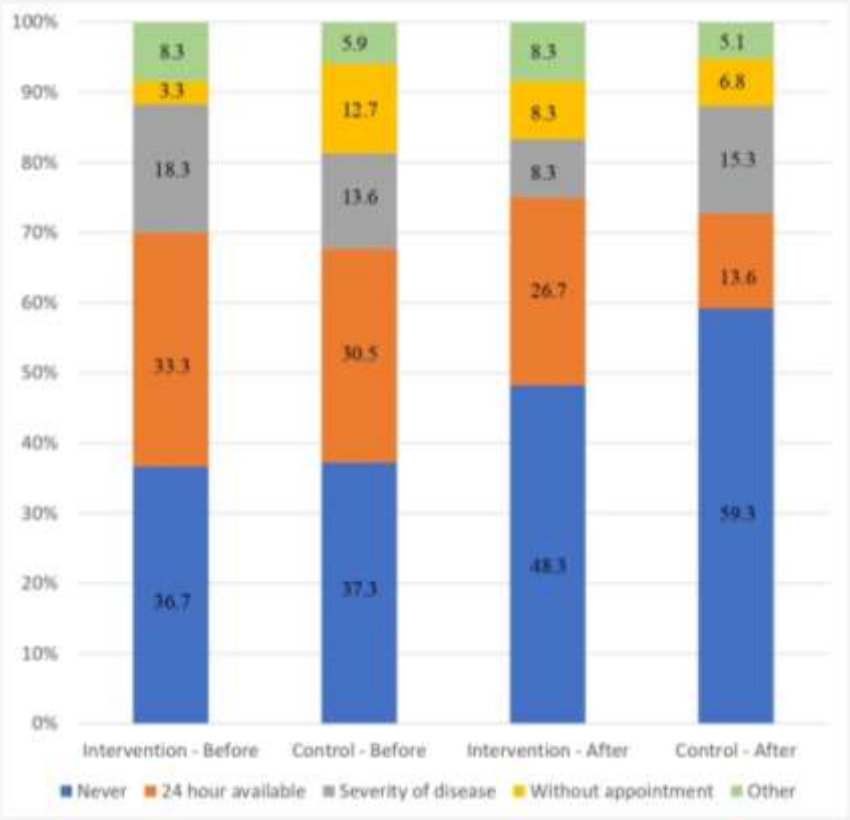

Figure 2. Reasons the mother to apply to the emergency service for her child.

The approach to the febrile child was questioned and the frequency of antipyretic drug administration decreased significantly in both groups after the intervention (Intervention: p<0.001; Control: p=0.007). Table 5 shows the comparisons for both groups before and after the intervention for each approach.

Propositions about how mothers manage RTIS were asked again, and the Cronbach-alpha coefficient, which shows the internal consistency of the scale after the intervention, was calculated as 0.717. Although KAB score changes (delta score) were higher in the intervention group, there was no statistically significant difference (Table 6).

Table 5. Comparison of the practices of mothers for their children in case of fever in the intervention and control groups before and after the intervention

		Intervention (N=60)			**Control (N=118)**		
***Number (Percentage)**		**Before n (%)**	**After n (%)**	**P value***	**Before n (%)**	**After n (%)**	**p value***
Take to doctor immediately	Yes	16 (26.7)	1 (1.7)		45 (38.1)	3 (2.5)	
	No	44 (73.3)	59 (98.3)	**<0.001***	73 (61.9)	115 (97.5)	**<0.001***
Put wet cloth on body	Yes	21 (35.0)	16 (26.7)		46 (39.0)	31 (26.3)	
	No	39 (65.0)	44 (73.3)	0.424	72 (61.0)	87 (73.7)	**0.033***
Put cloth with vinegar on body	Yes	10 (16.7)	4 (6.7)		12 (10.2)	5 (4.2)	
	No	50 (83.3)	56 (93.3)	0.070	106 (89.8)	113 (95.8)	0.065
Cover body	Yes	0	0	1.000	0	0	1.000
	No	60	60		118	118	
Take off clothes	Yes	26 (43.3)	28 (46.7)	0.839	50 (42.4)	46 (39.0)	0.607
	No	34 (56.7)	32 (53.3)		68 (57.6)	72 (61.0)	
Give bath	Yes	43 (71.7)	35 (58.3)	0.096	80 (67.8)	70 (59.3)	0.144
	No	17 (28.3)	25 (41.7)		38 (32.2)	48 (40.7)	
Give medication	Yes	57 (95.0)	36 (60.0)	**<0.001***	92 (78.0)	74 (62.7)	**0.007***
	No	3 (5.0)	24 (40.0)		26 (22.0)	44 (37.3)	
Wait without doing anything	Yes	1 (1.7)	0	1.000	2 (1.7)	0	0.500
	No	59 (98.3)	60		116 (98.3)	118	

* *McNemar* test

Table 6. Comparison of the intervention and control groups in terms of knowledge, attitude and behavior scores related to respiratory tract infection symptoms

	Intervention (N=60)		**Control (N=118)**		**p value**
	Mean ± StD	Median (IQR)	Mean ± StD	Median (IQR)	
First score	76,91±5,60	77(73-80)	76,88±5,21	76(74-80)	0,670*
Last score	83,58±6,76	84(78-89)	82,16±6,70	83(76-88)	0,193*
p value**	**<0,001****		**<0,001****		
Delta score	6.27±5.6 (min: -7 max:17)		5.17 ±6.2 (min: -16 max:20)		0.251***

* Mann-Whitney U comparison test in independent groups
** Wilcoxon comparison test in dependent groups
*** T-test in independent groups

DISCUSSION

As the primary outcome of this study, it was aimed to reduce unnecessary emergency department admissions due to respiratory tract infection symptoms in 6m-6y children, with the education given to mothers during their visits to the FHC. However, after the intervention, the frequency of admission to the ED with RTIS decreased for both groups, and also more in control group. The secondary results of the study were aimed to increase the knowledge of mothers about RTIS, to develop their expected attitudes, to change the perception of them preferring ED instead of FHC, and to increase the confidence in the active role of FP in the management of RTIS. At the end of the study, it was observed that the KAB scores of the mothers about RTIS increased significantly in both groups after the intervention. It was observed that trust in FP had increased, especially in the intervention group, and there had been a change in perception regarding the preference of FHC instead of ED for RTIS.

Learning about RTIS alarm findings during the intervention may have had an unexpected stimulating effect on mothers in the intervention group and increased their sensitivity about going to the ED. The scale which was applied to the control group before and after the intervention about KAB about RTIS (KABaRTIS), may have increased the awareness of mothers in the control group and may had an effect that caused the difference between the groups to be erased. This situation is also called the Hawthorne effect in literature (18). This result is also discussed in terms of contamination bias between the intervention and control groups, the content of the evaluation questions, the social spread of the expected change in the people in the same environment, the possibility of accessing the intervention material and peer education (19-21).

The risk of contamination was tried to be minimised with some measurements mentioned in the method section. Nevertheless, the fact that the control group was selected from the same FHC suggests the possibility of contamination risk. However, intervention studies with a similar method have been found in the literature (22,23).

While the frequency of mothers who stated that they applied to the ED due to the severity of the disease in the intervention group decreased, it increased in the control group. This suggests that there should be more than one variable that measures the effectiveness of the intervention, and that effectiveness should not only be measured by the number of admissions. In addition to this sharp quantitative outcome variable, qualitative outcomes may also determine the effectiveness of the intervention. The education method chosen as the intervention is aimed to be simple and easily applicable by every family physician in daily practice. However, the duration and number of the sessions are the most important factors affecting the effectiveness of the education. While such an example of intervention is not encountered in Türkiye, there are studies in other countries with a longer education period. However, there is no certainty about the minimum duration of education that should be planned for the intervention to be effective. For example, an intervention in which parents were given 90-minutes of education, and there was a significant difference in KAB scores in the evaluation made immediately after the intervention, but 6-months later, the attitude difference after the intervention for fever and RTIS management lost its significance. So even when the training is 90-minutes instead of 15-minutes, mothers may not give up on their habits (24). Therefore, it may be necessary to try different methods together for behavior change, such as adding a session in which the education content is reminded by phone call or text messages. In a systematic review evaluating educational interventions in terms of reminders, it is stated that reminders through various means such as letters, telephone calls, messages, and feedback increase the effectiveness of the intervention (25).

Researchers preferred a more cost-effective method in terms of reproducibility and generalizability of the study, and the use of brochures is a common design in previous studies. Moreover, there are other educational interventions in other areas that are considered effective and are conducted just by handing out brochures (26,27).

It was determined that the KABaRTIS score of mothers who were given brochures, increased. However, an increase in the scores measuring KAB does not guarantee a decrease in unnecessary emergency admissions. It is seen that the information is not directly reflected in the behavior.

Similar results were also found in literature (12,24,28).

Another reason may be the high education level of the study population. According to the 2022 data of the Turkish Statistical Institute, the frequency of women with high school or higher education in Türkiye is 37.13%, and in this research is 76.7% for intervention group. While the prevalence of women with 14 years or more education in Türkiye is 17.32%, it was found to be 43.1% in this research population (29). It has been shown that there is an inverse correlation between education level and unnecessary use of emergency services (30). Similar results were found in this study as well. This may have eroded the effectiveness of the intervention.

In some studies, with multiple training sessions, the expected effect was reported (12). However, as the follow-up period or the number of sessions in multi-session intervention studies increased, the number of participants that were reached and continued the study decreased (31).

Considering the findings of this study, mothers seem to be conscious about the management of fever at home. However, the most common reason for applying to the ED is sustained fever outside of the working hours of the FHC. Similar findings are consistent with other studies conducted both in Türkiye and in the world. While some countries are trying to solve this problem with the gatekeeping FM model, in which they add the possibility of 24-hour access to primary care, some health systems use methods such as providing health services by telephone or not covering non-emergency ED admissions by insurance (22,24,32,33). In a systematic review, out of 39 interventions, it was stated that unnecessary visits to emergency services were reduced in approximately two-thirds of the articles scanned (34).

Strengths and Weaknesses: When the Turkish medical literature is examined, no intervention studies were found on reducing unnecessary admissions to ED in children with RTIS. This is the first of all.

The research design was planned as single-blind with a control group. The final evaluation data were collected by a researcher who did not know which participants had the intervention. In addition, the fact that the mothers did not know which group they belonged to, made them semi-blind.

For allocating, the unit randomly assigned to the researcher for the intervention. There was no difference between these two groups in terms of sociodemographic characteristics, data on the use of health services, and KABaRTIS scores in the first evaluation. The data of the study were collected in the same seasons to minimize seasonal effects. However, only people who came to the FHC and volunteered were included in the intervention and this may have created selection bias.

The number of health care admissions and their reasons depend on the mothers' statements, leading to the possibility of recall bias. However, there are other studies in literature evaluating the results based on the mothers' statements.

There is no Turkish or English scale that measures KABaRTIS, for which validity and reliability studies have been conducted. For this reason, KAB of the intervention and control group participants was compared with the scale prepared by the researchers using expert opinion and guidelines.

In this research, a brochure was used as a visual material. It was not diversified according to the knowledge level of the mothers. Standardization of education was considered as a strength, but mothers' learning needs regarding RTIS may differ. In this case, the probability of benefiting from education may have been lower for some women.

CONCLUSION

The primary result expected in this research is a hard quantitative variable affected by many non-modifiable factors such as FHC working hours, lack of referral chain, increasing knowledge level not being sufficient for behavior change. The secondary outcomes are qualitative variables affected by more modifiable factors. While the frequency of unnecessary visits to the ED with RTIS did not decrease at the expected level in the intervention group, it was observed that it was beneficial in terms of increasing the expected KABaRTIS, and increasing confidence in the FP.

Strengthening FM and the doctor-patient relationship can play a key role in resource management. Healthy child follow-ups provide a great opportunity for mothers to improve their knowledge, attitudes, and behaviors. However, since increasing the level of knowledge is not enough to change habits, it is necessary to use different training methods that can affect attitudes and behaviors.

With a longer intervention, consisting of multiple sessions, including reminders, and regular follow-ups by the FP, it may be possible to reduce unnecessary ED visits and provide a permanent change in behavior. For this purpose, an intervention can be planned with a larger sample, randomly selected mothers from different populations, by allocating a large budget and combining different methods. Considering the characteristics of adult education, more interactive interventions can be planned where the participants are not only listeners.

This study is important in terms of being the first of the educational interventions in Türkiye in order to reduce unnecessary ED admissions with RTIS in children. However, more comprehensive, and long-term studies should be designed in order to see the expected decrease permanently.

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RESEARCH ARTICLE

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Evaluation of Serum Annexin A1 Values in Patients with Inflammatory Bowel Diseases

ABSTRACT

Objective: Annexin A1(AnxA1) is an anti-inflammatory mediator. In the current study,we aimed to evaluate whether or not serum Annexin A1 levels of inflammatory boweldiseases (IBDs) patients relate to the clinical and laboratory traits of IBDs.

Materials and Methods: This case-control study included 67 ulcerative colitis (UC) patients, 53 Crohn's disease (CD) patients and 60 healthy controls. The Mayo Clinical scoring system (MCS) was used for UC and the histological activity index (HAI) was determined by Truelove and Richards method. The Crohn's disease activity index (CDAI) was used for CD patients. Montreal classification was used for the localization of IBDs.

Results: The mean serum AnxA1 concentrations were not statistically significant in UC, CD and the control groups (26.36±17.30 ng/ml vs 22.98±12.74 vs 24.45±12.18 ng/ml respectively, *p=0.404*). The MCS, HAI of UC patients negatively correlated with the serum AnxA1 values (rho=-0.616, *p<0.001 vs* rho=-0.778, *p<0.001* respectively). UC patients with limited disease had higher values than those with extensive disease (19.5 (IQR:14.5–47.8) ng/ml vs.13.4 (IQR:10.8–18.4) ng/ml respectively, *p=0.002*). In CD patients, CDAI values negatively correlated to the serum AnxA1 values (rho=-0.770, *p<0.001*).

Conclusions: Serum AnxA1 values might be an auxiliary biomarker for the disease activity in patients with IBDs.

Keywords: Inflammatory Bowel Disease, Annexin A1.

İnflamatuvar Bağırsak Hastalıklarında Serum Annexin A1 Düzeylerinin Değerlendirilmesi

ÖZET

Amaç: Annexin A1 (AnxA1) anti-inflamatuar bir moleküldür. Çalışmamızda, inflamatuar barsak hastalıklarında (İBH) serum Annexin A1 düzeylerinin hastalıkların klinik ve laboratuvar özellikleri ile ilişkili olup olmadığı araştırılmıştır.

Gereç ve Yöntem: Bu vaka-kontrol çalışmasına 67 ÜK hastası, 53 Crohn hastalığı (CH) hastası ve 60 sağlıklı kontrol dahil edilmiştir. ÜK klinik aktivitesi için Mayo klinik skorlama sistemi (MKS) kullanıldı, histolojik aktivite indeksi (HAİ) Truelove ve Richards yöntemiyle belirlendi. CH için Crohn hastalığı aktivite indeksi (CHAİ) kullanıldı. İBH lokalizasyonu için Montreal sınıflandırması kullanıldı.

Bulgular: ÜK, CH ve kontrol grupları arasında ortalama serum AnxA1 konsantrasyonları yönünden fark saptanmadı (26,36±17,30 ng/ml vs 22,98±12,74 vs 24,45±12,18 ng/ml, sırasıyla *p=0,404*). ÜK'de MKS, HAİ ve serum AnxA1 değerleri arasında negatif korelasyon tespit edildi (rho=-0,616, p<0,001 vs rho=-0,778, sırasıyla *p<0,001*). Sınırlı hastalığı olan ÜK hastalarında, yaygın hastalığı olanlara göre daha yüksek serum AnxA1 değerleri bulundu (19,5 (IQR:14,5–47,8) ng/ml ve 13,4 (IQR:10,8–18,4) ng/ml, sırasıyla *p=0,002*). CH'da serum AnxA1 değerleri ile CHAİ arasında negatif korelasyon bulundu (rho=-0,770, *p<0,001*).

Sonuç: Serum AnxA1 düzeyleri İBH'da hastalık aktivite tespiti için yardımcı bir biyobelirteç olabilir.

Anahtar Kelimeler: İnflamatuar Barsak Hastalığı, Annexin A1.

INTRODUCTION

The prevalence of inflammatory bowel diseases (IBDs) is increasing and they result in growing socioeconomic burden. In recent years, researches on various prognostic, diagnostic and therapeutic molecules have gained interest based on the pathogenicity of IBDs (1,2).

The resolution process makes acute inflammation unnoticeable and self-limited without progressing to the chronic phase and it is a normal protective response (3). The failure of resolution leads to chronic inflammation and tissue damage (4). Resolution is mainly directed by biochemical molecules and specialized pro-resolving mediators (SPMs) including resolvins, galectins, lipoxins, annexins and protectins. SPMs are synthesized by the effect of neutrophils and macrophages, and they exert anti-inflammatory activity (2).

Annexin A1 (AnxA1) is a resolution-associated calcium and phospholipid binding protein and in general, it is reported to have anti-inflammatory activity. AnxA1 mediates the majority of its effects through formyl peptide receptors (FPRs). It is related to mucosal regeneration and healing (5,6). AnxA1 has a well-defined anti-inflammatory role in the innate immune system but the pro-inflammatory role of AnxA1 is also pronounced (7,8).

The therapeutic efficacy of AnxA1 is also another concern (2,8). Growing evidence exists about the role of AnxA1 in chronic inflammatory diseases and cancer, but the role of AnxA1 in these diseases is not entirely clear (8).

There is a scarcity of data about the role of AnxA1 in IBDs and the results of the reports are variable. Furthermore, the role of AnxA1 in the disease activity of IBDs is not clear (5,9-13). With regard to this, we aimed at evaluating whether serum levels of AnxA1 in patients with IBDs could serve as a biomarker by using the different clinical and endoscopic disease activity assessment models along with the histological activity in UC patients according to Truelove and Richards method.

MATERIAL AND METHODS

Study Population: The study included 67 patients with ulcerative colitis (UC), 53 patients with Crohn's disease (CD) and 60 healthy controls, admitted to the Gastroenterology department of our institute between January 2023 and May 2023. The Local Ethics Committee approved the study (11.01.2023/05). Written informed consent was obtained from all participants. Participants with clinical conditions that can affect serum AnxA1 levels such as sepsis, any malignancies, cardiac failure, chronic renal disease were excluded from the study. Participants with severe organ failure, acute or chronic infections, autoimmune diseases, or gut resection were also excluded from the study. The healthy control group included participants who underwent a colonoscopy for indications other than IBDs and whose colonoscopy results were normal.

The disease duration, medications for IBDs, comorbidities, extra-intestinal manifestations, IBDs in first degree relatives in the patients were recorded. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and other biochemical tests were measured before endoscopic examination**.**

Assessment of the Clinical and Endoscopic Activities: The Mayo Clinical score (MCS) was applied for the patients with UC and was scored between 0-12. Scores of ≤2 were classified as clinical remission whereas scores of >2 indicated an activation [14]. The Crohn's disease activity index (CDAI) was used to assess the disease activity in the patients with CD and scores of <150 were noted as clinical remission whereas scores of ≥150 were noted as activation (15).

The disease extent of the patients with IBDs was defined in agreement with the Montreal classification (16). In UC, proctitis and left-sided colitis were recorded as limited disease, whereas extensive pancolitis was recorded as extensive disease. Mayo endoscopic activity scoring (MES) index was used for the endoscopic activation of UC and was classified as remission (0), mild (1), moderate (2) and severe (3) colitis. Scores of (0) and (1) were recorded as inactive disease whereas (2) and (3) were recorded as active disease (14). The localization of CD was classified as ileal, colonic or ileocolonic disease (16).

Histopathologic Evaluation in Ulcerative colitis: The same pathologist who was blind to the participants evaluated the formalin-fixed, paraffin-embedded, and H&E-stained colonic biopsies of the UC patients and performed grading through a scale similar to that developed by Truelove and Richards. Active inflammation, chronic inflammation and crypt distortion were the components of the scale. The histopathologic activity index (HAI) was defined as the sum of the scores of these components (17).

Measurement of Serum Annexin-A1: The serum for AnxA1 was separated from venous blood samples and after centrifugation at 5000×g for 10 minutes at 30°C, the supernatant serum was stored at (−) 80°C until analysis for 6-9 months. The commercially available Human Annexin A1 Bioassay Technology Laboratory Kit (Cat. No. E3288Hu, Lot:202302004) was used for the ELISA measurement of the serum annexin A1 (Intra-Assay: CV <8 %, Inter-Assay: CV <10 %) with a microplate reader (Biotech Epoch 2 Microplate ELISA Reader, USA).

Statistical Analysis: Statistical analyses were performed using the IBM SPSS software version 26.0. Descriptive analyses were presented using proportions for categorical variables and using medians and inter-quartile range (IQR) /mean±standard deviation for continuous variables.

The variables were investigated using Kolmogorov Smimirnov test to determine whether or not they were normally distributed. Comparisons were performed using the Mann-Whitney U test for continuous variables between two groups. Kruskal Wallis H tests were conducted to compare for continuous variables among three groups. Post hoc tests were performed using Bonferroni correction to adjust for multiple comparisons. Comparisons were performed using the chi-square test for categorical variables. The correlation coefficients and their significance were calculated using the Spearman test.

The capacity of serum AnxA1 values in predicting presence for the Mayo clinical scoring (Activation–Remission) of ulcerative colitis and for Crohn's Diaease Acitivity Index (Activation–Remission) of Crohn's disease was analyzed using ROC (Receiver Operating Characteristics) curve analysis. Their outcomes were presented as AUC (Area under the curve), criterion (cut off), sensitivity and specificity values. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

In total, 67 UC patients (47 males and 20 females), 53 CD patients (37 males and 16 females) and 60 healthy controls (36 males and 24 females) participated in the study. Demographic, clinical and laboratory characteristics of the participants are presented in Table 1. The groups were similar with respect to age and gender. The disease duration in the patients was also similar. CRP, ESR and neutrophil values were higher in the patients with IBDs but WBC values were not different in the three groups (*p>0.05*). It was determined that 35.8 % of the patients with UC were not under treatment whereas 41.5 % of the patients with CD were not taking any medication (Table 1).

Table 1. Demographic, clinical and laboratory characteristics of the study population.

	UC Patients n=67	**CD Patients n=53**	**Control Group n=60**	**p value**
Gender, n (%)				
Female	20 (29.9)	16 (30.2)	24 (40.0)	0.406*
Male	47 (70.1)	37 (69.8)	36 (60.0)	
Age (years), median (IQR)	35 (26-50)	36 (25-48)	39 (29-51)	0.302[#]
Disease duration (years), median (IQR)	2 (0.5-5)	1.5 (0-4.5)		0.189[&]
CRP (mg/L), median (IQR)	23.5 (2.7-40.1)	9.5 (2.5-30.8)	2.7 (0.9-4.6)	<0.001[1,#]
ESR (mm/h), median (IQR)	35.0 (14.0-60.0)	31.0 (18.0-50.0)	9.50 (3.0-17.8)	<0.001[2,#]
WBC ($x10^3/\mu L$), median (IQR)	8.0 (6.6-9.7)	8.4 (6.9-11.2)	7.6 (6.2-8.9)	0.081[#]
Neutrophils ($x10^3/\mu L$), median (IQR)	5.1 (3.8-6.7)	6.2 (4.5-8.7)	4.6(3.7-5.7)	0.003[3,#]
Serum Annexin A1 (ng/ml), mean(sd)	26.36 (17.30)	22.98 (12.74)	24.45 (12.18)	
Serum Annexin A1 (ng/ml) median (IQR)	17.1 (12.7-45.9)	20.4 (11.8-35.7)	18.2 (15.2-35.1)	0.404 [#]
Localization of UC, n (%)				
Limited disease	47 (70.1)			
Extensive disease	20 (29.9)			
Localization of CD, n (%)				
Ileal	35 (66.1)			
Colonic	6 (11.3)			
Ileocolonic	12 (22.6)			
Mayo Endoscopic Score of UC, n (%)				
Inactive disease	22 (32.8)			
Active disease	45 (67.2)			
Treatment of the patients, n (%)				
No treatment	24 (35.8)	22 (41.5)		<0.001*
Only 5-ASA	28 (41.8)	3 (5.7)		
5-ASA±Az±S	10 (14.9)	16 (30.2)		
BA+other agents	5 (7.5)	12 (22.6)		
IBDs in first degree relatives, n (%)	9 (13.4)	10 (18.9)		
Mayo Clinical Score of UC, median (IQR)				
Remission (score ≤ 2), n (%)	18 (26.9)			
Activation (score>2), n (%)	49 (73.1)			
Histological Acitivity Index in UC, median (IQR)	6 (3-7)			
Crohn's Diaease Acitivity Index				
Remission (score <150), n (%)	21 (39.6)			
Activation (score≥150), n (%)	32 (60.4)			
Extraintestinal Manifestations n (%)	8 (11.9)	18 (34.0)		0.004*

Abbreviations: CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IQR: Inter quartile range; WBC: White blood cells; UC: Ulcerative colitis; CD: Crohn's disease; 5-ASA:5-aminosalycilate; Az: Azathioprine, S: Steroid, BA: Biological agents, IBDs: Inflammatory bowel diseases. sd: standard deviation, IQR: İnterquartile range.

Footnotes: [1] Significant difference in comparison of UC vs controls, CD vs controls (p<0.001, p<0.001); [2]Significant difference in comparison of UC vs controls, CD vs controls (p<0.001, p<0.001); [3]Significant difference in comparison of CD vs controls (p=0.002).

* Chi-square test [&] Mann-Whitney U test [#] Kruskal-Wallis test

Although the mean serum AnxA1 concentrations were higher in the patients with UC compared to CD patients and the control group, the differences were not statistically significant (26.36±17.30 ng/ml vs 22.98±12.74 vs 24.45±12.18 ng/ml respectively, *p=0.404*). The mean serum AnxA1 value was the lowest in the patients with CD (Table 1).

The patients with UC who were in remission had higher serum AnxA1 concentrations than those having clinically active diseases (51.6 (IQR:44.1–56.2) ng/ml vs. 15.3 (IQR:11.5–19.3) ng/ml respectively, *p<0.001*). UC patients with limited disease also had higher AnxA1 values than those with extensive disease (19.5 (IQR:14.5–47.8) ng/ml vs.13.4 (IQR:10.8 – 18.4) ng/ml respectively, *p=0.002*). According to endoscopic activity scores, UC patients having inactive diseases had higher AnxA1 values than the patients having active diseases (47.4 (IQR:35.1-55.9) ng/ml vs. 15.3 (IQR:11.5–19.3) ng/ml respectively, *p<0.001*). The median serum AnxA1 values were similar in UC patients with respect to treatment status and modalities, extra-intestinal manifestations and family history of IBDs (Table 2).

Table 2. Serum Annexin A1 values according to the disease phenotype and treatment modalities in the patients with IBDs.

				Serum Annexin A1 (ng/ml)			
		n	**%**	**Median**	**IQR**		**p**
Ulcerative Colitis							
Treatment status	No treatment	24	35.8	17.8	14.3	45.4	
	Under treatment	43	64.2	17.1	12.7	45.9	0.969[&]
Treatment modalities	No treatment	24	35.8	17.8	14.3	45.4	
	Only 5-ASA	28	41.8	17.5	13.2	47.3	
	5-ASA±Az±S	10	14.9	15.2	12.4	23.9	
	BA+other agents	5	7.5	41.7	9.8	49.6	0.890[#]
Mayo clinical scoring	Remission (score ≤ 2)	18	26.9	51.6	44.1	56.2	
	Activation (score >2)	49	73.1	15.3	11.9	19.4	<0.001[&]
Localization of UC	Limited disease	47	70.1	19.5	14.5	47.8	
	Extensive disease	20	29.9	13.4	10.8	18.4	0.002[&]
Mayo endoscopic activity	Inactive disease	22	32.8	47.4	35.1	55.9	
	Active disease	45	67.2	15.3	11.5	19.3	<0.001[&]
IBDs in first degree relatives	Positive	58	86.6	16.4	12.6	42.8	
	Negative	9	13.4	22.8	16.0	55.5	0.162[&]
Extra-intestinal Manifestations	Positive	59	88.1	18.8	13.2	46.8	
	Negative	8	11.9	14.7	11.0	19.3	0.209[&]
Crohn's disease							
Treatment status	No treatment	22	41.5	17.7	9.4	26.7	
	Under treatment	31	58.5	20.8	12.3	37.4	0.112[&]
Treatment modalities	No treatment	22	41.5	17.7	9.4	26.7	
	Only 5-ASA	3	5.7	30.6	14.9	39.7	
	5-ASA±Az±S	16	30.2	20.6	13.4	38.5	
	BA+other agents	12	22.6	20.5	9.1	37.0	0.293[#]
Crohn's disease activity index	Remission (score<150)	21	39.6	36.3	31.4	40.8	
	Activation (score≥150)	32	60.4	12.2	9.1	18.9	<0.001[&]
Localization of CD	Ileal	35	66.1	22.3	12.1	36.0	
	Colonic	6	11.3	15.2	9.4	34.7	
	Ileocolonic	12	22.6	16.0	11.0	33.5	0.727[#]
IBDs in first degree relatives	Positive	43	81.1	20.8	12.1	36.0	
	Negative	10	18.9	12.5	8.5	33.1	0.211[&]
Extra-intestinal Manifestations	Positive	35	66.0	24.7	12.8	36.2	
	Negative	18	34.0	13.6	9.1	31.4	0.102[&]

Abbreviations; IQR: Inter quartile range; UC: Ulcerative colitis; CD: Crohn's disease; IBDs: Inflammatory bowel diseases. 5-ASA:5-aminosalycilate; Az: Azathioprine, S: Steroid, BA: Biological agents,
Footnotes: [&] Mann-Whitney U test [#] Kruskal-Wallis tes

There were strong and negative correlations between CRP and HAI values of UC patients and serum AnxA1 values (rho=-0.723, *p<0.001* vs rho=-0.778, *p<0.001* respectively). ESR, leucocyte, neutrophil and MCS values of UC patients were also inversely correlated to the serum AnxA1 concentrations whereas the disease duration was positively correlated (Table 3).

Table 3. Correlations between the serum Annexin A1 values and the clinical, laboratory variables of the patients with inflammatory bowel diseases

Serum Annexin A1 **(ng/ml)**	**rho***	**p**
Ulcerative Colitis (n=67)		
CRP (mg/L)	-0.723	<0.001
ESR (mm/h)	-0.546	<0.001
Leucocyte (x10^3/μL)	-0.425	<0.001
Neutrophil (x10^3/μL)	-0.413	0.001
Mayo clinical scoring	-0.616	<0.001
Histological activity index	-0.778	<0.001
Disease duration (years)	0.248	0.043
Crohn Disease, (n=53)		
CRP (mg/L)	-0.583	<0.001
ESR (mm/h)	-0.558	<0.001
Leucocyte (x10^3/μL)	-0.189	0.175
Neutrophil (x10^3/μL)	-0.206	0.139
Crohn's disease activity index	-0.799	<0.001
Disease duration (years)	0.214	0.124

Abbreviations: CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.
Footnotes: *Spearman correlation coefficient

The patients with CD who were in remission had higher serum AnxA1 values than the patients having clinically active disease (36.3 (IQR:31.4-40.8) ng/ml vs. 12.2 (IQR:9.1-18.9) ng/ml respectively, *p<0.001*). In terms of disease localization, treatment status and modalities, extra-intestinal manifestations and family history of IBDs in CD patients, there was no statistically significant difference with respect to median serum AnxA1 values (*p>0.05*) (Table 2). There was strong and negative correlation between CDAI of CD patients and serum AnxA1 values (rho=- 0.799, *p<0.001*). CRP and ESR values also inversely correlated with serum AnxA1 concentrations in CD patients (Table 3).

The receiver operating characteristic curve (ROC) analysis revealed that the area under curve (AUC) for AnxA1 concentrations had a 0.901 (95%CI: 0.805-0.998, *p<0.001*) diagnostic accuracy for the clinical activity of UC (MCS). The sensitivity and specificity for the cut-off level of ≤34.9 ng/ml were 88.9% and 89.8 %, respectively (Figure 1).

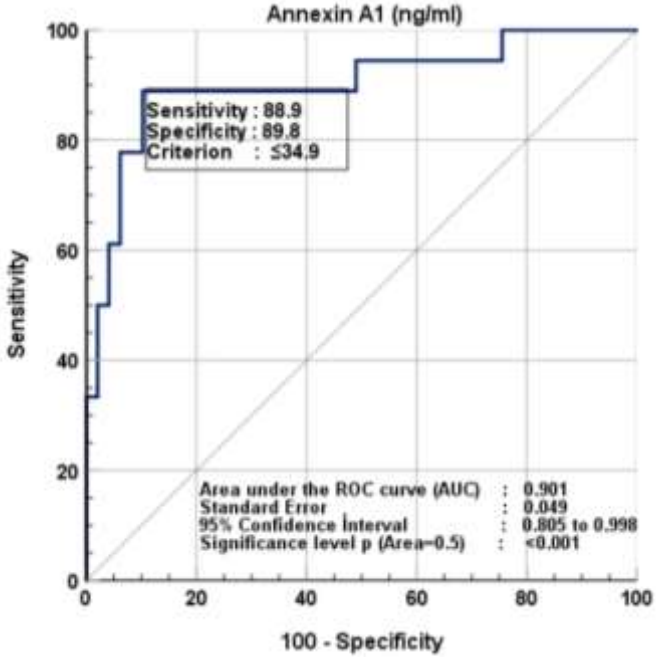

Figure 1. ROC curve analyses of the predictive values of serum Annexin A1 concentrations for the Mayo clinical scoring of ulcerative colitis.

The ROC analysis also revealed that the AUC for AnxA1 concentrations had a 0.972 (95%CI: 0.931-1.000, *p<0.001*) diagnostic accuracy for the clinical activity of the disease in CD (CDAI), and the sensitivity and specificity for the cut-off level of ≤25.2 ng/ml were 95.2 % and 93.7 %, respectively (Figure 2).

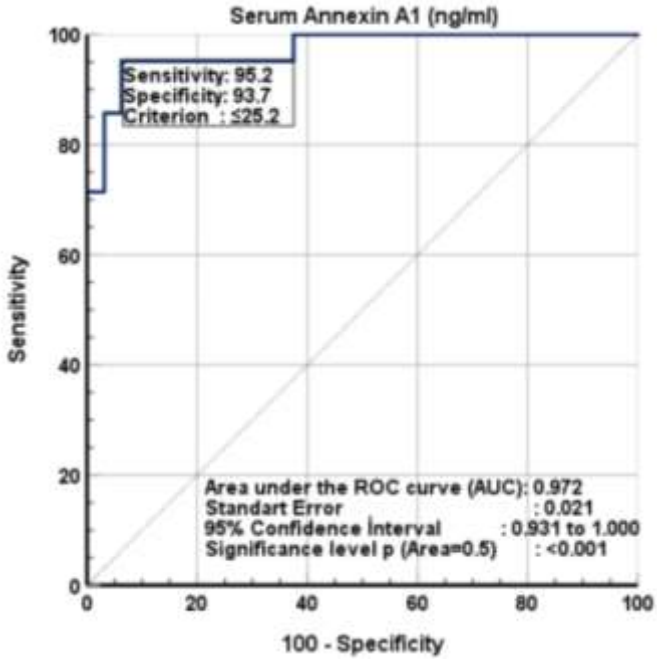

Figure 2. ROC curve analyses of the predictive values of serum Annexin A1 concentrations for the Crohn's Diaease Activity Index of Crohn's disease.

DISCUSSION

The pathogenesis of inflammatory bowel diseases (IBDs) is not exact and heterogeneous. The immune dysregulation of the enteric microbiota is believed to be the major pathogenic mechanism in IBDs. It is worthy of note that IBDs have relapsing and remitting phases (18).

Annexin-A1 (AnxA1) is a 37 kDa protein and it is also known as lipocortin 1. This molecule has diverse biological actions. The expression of AnxA1 is induced by glucocorticoid signaling and it inhibits the activity of cytosolic phospholipase A2 and cyclooxygenase 2, thus exhibiting anti-inflammatory, anti-pyretic, and anti-hyperalgesic activities. It is abundant in monocytes, macrophages and neutrophils (19).

Neutrophilic infiltration into the gut wall is the mainstay of the histopathological features in IBDs (5,18,20). Neutrophils are reported to be the main source of AnxA1 in the inflamed mucosa of experimental colitis model in rats (21)**.** As a pro-resolving mediator, AnxA1 enhances mucosal wound repair via inhibiting neutrophil recruitment to the inflamed area. It also induces neutrophil clearance (8,19).

Vong et al. (9) examined the colonic mucosal biopsies of inactive and active UC patients, and healthy controls by using fluorescence microscopy. After biopsies were performed on patients with active disease, Vong et al reported that the neutrophils in the biopsies were stained by marked AnxA1. In this study, AnxA1 expression was not limited to cells infiltrating the lamina propria but was also detected in epithelial cells lining the intestinal crypts in the biopsies of active UC patients. The over-expression of the molecule was ascribed to the protective function of AnxA1 for mucosal homeostasis (9). We also reported higher serum neutrophil values in the patients with IBDs compared to the healthy controls and this results confirm the increased neutrophil activity in IBDs.

Although AnxA1 is generally reported to have anti-inflammatory properties in some diseases, it has alternating roles being discussed within the same disease, as well as within different disease subsets (8). There are a limited number of studies evaluating the role of AnxA1 in IBDs. The methods used in and the results of these studies are different (5,9-13).

Kourkoulis et al. (10) evaluated the serum AnxA1 values of UC patients (n=42) and healthy controls (n=14). They reported higher serum AnxA1 values compared to the healthy controls and proposed serum AnxA1 values as a diagnostic biomarker of UC. On the other hand, Sena et al. (11) detected lower levels of plasma AnxA1 in CD patients (n=28) compared to the healthy controls (n=12). Vong et al. (9) reported that immunofluorescence detection of AnxA1 in colonic biopsies of the participants demonstrated increased expression in patients with UC, whether active

(n=8) or in medically-induced remission (n=16) compared to healthy controls (n=20).

In our study, the mean serum AnxA1 concentrations were higher in the patients with UC but lower in CD patients compared to the healthy control group. However, these results are not statistically significant. Different AnxA1values in three studies may partly be due to the different numbers of the subjects evaluated in the studies and we think that larger sample-sized cohorts might affect the statistical significance and they can reveal significant results which could be clinically important.

Medications aim to suppress the immune activation in IBDs and they might affect AnxA1 activation because AnxA1 expression is induced by glucocorticoid signaling and depends on the neutrophilic activity which has a key role in AnxA1 expression (8,19). 64.2 % of UC patients and 58.5 % of CD patients in our study were under treatment. In the study of Sena et al. (11), CD patients who were successfully treated with infliximab were reported to have higher regulated plasma AnxA1 expressions and it was concluded that loss of AnxA1 expression may support inflammation during CD and can serve as a biomarker of disease progression. Also, changes in AnxA1 levels may be predictive of therapeutic efficacy for infliximab.

In another study, it was also concluded that infliximab induces AnxA1 expression and secretion in activated intestinal leukocytes (13). We think that AnxA1 expression might be altered by these medications (19,21). Neutrophil counts in the patients with IBDs were higher than the healthy controls in our study but serum AnxA1 values in three groups were not statistically different. This result may be a pointer to the effect of medications on the neutrophil activity which plays a role in AnxA1 expression. In addition, the ratios of the patients with IBDs who were not under treatment could not be ignored in the current study but no statistically significant differences were noted in the patients who were not under treatment and those who were.

We also did not detect any differences according to serum AnxA1 concentrations in the patients using different treatment modalities. In the current study, most of the patients with UC were on 5-ASA therapy while most CD patients were on immuno-suppressive therapy, and the ratio of the patients taking biological agents was the lowest in both groups, especially in UC. The groups of patients were heterogeneous according to the treatment modalities and we think that larger sample sized cohorts including equal numbers of patients with respect to different treatment modalities could reveal significant results. To exclude the effect of medications on the serum values of AnxA1, newly diagnosed patients with IBDs not taking any medications can be evaluated for the diagnostic accuracy of serum AnxA1, and this may be another subject for further investigations.

Kourkoulis et al. (10) also evaluated the association between UC endoscopic activity scores according to MES index and serum AnxA1 concentrations as in our study. They detected no statistical difference between the endoscopic activity and serum AnxA1 concentrations, but in that mentioned study, the number of UC patients especially in the patients with active endoscopic disease (MES 2 and 3) was very small. We reported higher serum AnxA1 values in UC patients who had inactive diseases than those with active diseases. In terms of endoscopic findings, UC patients with limited disease also had higher values. These results may be attributed to the anti-inflammatory activity of AnxA1which limits the disease progression in UC. In CD patients, according to the localization of the disease, there was no statistically significant results in serum AnxA1 concentrations.

We noted negative correlations between CRP, ESR values and serum AnxA1 concentrations in the patients with IBDs. These correlations were stronger in UC patients. Sena et al. (11) also observed an inverse correlation between plasma CRP and plasma AnxA1. CRP and ESR are traditional acute phase reactants and inverse correlations between these tests and these results can be due to the lack of AnxA1 to exert an anti-inflammatory activity in IBDs.

The European Crohn's and Colitis Organization (ECCO) guidelines state that the treatment of IBDs should not only control the symptoms and that mucosal healing is the best therapeutic goal (22). Inflammation in the gut wall is also an indicator for the disease activity in patients with IBDs (23). De Paula-Silva et al**.** (13) evaluated the colon biopsies from CD untreated (n=4) and treated positive (n=3) or negative (n=2) responders to infliximab. They analyzed the colon biopsies by fluorescence intensity of staining and performed a histological grading. The dextran sulfate sodium (DSS) induced experimental colitis model was also used, and the healthy controls were also included in this group. In the study of de Paula-Silva et al**.** (13), the subjects were assigned into infliximab treated and non-treated groups. Histological grading was designed according to changes on crypts, architecture, edema, ulceration and presence of immune cells at the gut wall. Grades of 0, 1, 2, 3, and 4 were respectively attributed to normal, mild, mild–moderate, moderate–severe, and severe conditions. Results were expressed as the mean of total grading both in CD patients and the experimental colitis models.

The results of this study revealed that colonic AnxA1 expressions presented a strong negative correlation with the histological grading which means that the decrease of these markers is

associated with more tissue damage (13). We also reported strong negative correlations between the HAI scores and serum AnxA1 concentrations according to Truelove and Richards methods. In both studies, results can be ascribed to the protective effect of AnxA1 in IBDs. As a limitation, we did not apply histological grading system in the patients with CD. With regard to infliximab response in CD patients, de Paula-Silva et al. (13) reported that AnxA1 in blood did not correlate with CDAI and plasma levels of serum AnxA1 and might not be a reliable biomarker for remission or failure after infliximab treatment (responders, n=3 and non-responders, n=2). However, the number of the patients in that study was very small.

To the best of our knowledge, we firstly investigated the relations between the clinical activity scores and serum AnxA1 concentrations in the patients with IBDs. There were inverse correlations between these scores and serum AnxA1 values. These correlations were stronger in CD patients. With respect to MCS values in UC and CDAI in CD patients, serum AnxA1 concentrations in the patients who were in the clinical remission phases were higher. We think that serum AnxA1 values might be a good determinant of clinical activity in patients with IBDs.

For IBDs, AnxA1 was also declared as a therapeutic target (2,8). Today, current medical treatments for IBDs focus on the inhibition of immune activation but they cannot achieve complete remission (18). Topical delivery of AnxA1 into the gut mucosa might be an adjunctive treatment modality.

Several investigations have focused on the identification of biomarkers of disease progression that could be valuable in the diagnosis and treatment of IBDs. The patients with IBDs usually undergo invasive endoscopic procedures which can cause discomfort. The clinical, endoscopic and biochemical findings can be inconsistent with each other in IBDs. Searching for the ideal biomarkers correlating to all disease activity parameters, like fecal calprotectin, is important in IBDs (24).

The major limitation of the current study was the small number of the study population as it was a single-centered trial. Larger cohorts might reveal significant results about the diagnostic accuracy of serum AnxA1 values and they might also exhibit the effects of therapeutic agents on serum AnxA1 values. Comparing fecal calprotectin values with serum AnxA1 concentrations could be more valuable for the assessment of diagnostic and prognostic accuracy of serum AnxA1.

Diagnostic strategies with the possibility of therapeutic interventions can be developed by identifying new, practical and objective biochemical markers in IBDs. Serum AnxA1 can be a valuable biomarker for the clinical and laboratory traits of IBDs and it might be an auxiliary test for the assessment of disease activation. Further studies are needed to delineate the diagnostic and the therapeutic accuracy of serum AnxA1 in IBDs.

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RESEARCH ARTICLE

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Conventional and Diffusion MR Imaging Features of Ring-shaped Lateral Ventricular Nodules

ABSTRACT

Objective: The aim of this study is to evaluate the conventional and diffusion MRI findings of ring-shaped lateral ventricular nodules (RSLVN) along with clinical features.

Materials and Methods: MR images of all patients who underwent contrast-enhanced brain MRI between 2019 and 2023 were retrospectively evaluated. The number, shape, maximal diameter, and signal intensity of RSLVNs on T1-weighted (T1W), T2-weighted (T2W), fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI), and contrast-enhancement status were evaluated. Apparent diffusion coefficient (ADC) values and normalized ADC ratios of nodules were also determined. If follow-up MRIs were performed, morphological changes of RSLVNs were evaluated.

Results: RSLVN was observed in fifteen (0.51%) of 2920 patients. Multiple RSLVNs were observed in five patients and therefore a total of 23 RSLVNs were identified in fifteen patients. Nodules were located on the roof of the lateral ventricle in eight nodules (34.8%), in the frontal horn in twelve nodules (52.2%), and in the septum pellucidum in three. 6 of 23 RSLVNs (26.1%) were larger than 1 cm. All RSLVNs were isointense on T1W and T2W, while hyperintense on FLAIR. On DWI, 20 of 23 RSLVNs had isointense signal and the remaining 3 lesions were hyperintense. The mean ADC value and nADC ratio were 1.42 ± 0.29 × 10-3mm2 and 1.87 ± 0.31, respectively.

Conclusions: RSLVNs may be more frequent than previously reported. Their uniform MRI appearance and typical localizations are distinctive, and they can reach relatively large sizes. Morphological stability during follow-up and the ADC values of these lesions suggest a possible benign nature.

Keywords: RSLVN, Neuroimaging, Magnetic Resonance Imaging, Nodule, Lateral Ventricle.

Halka Şekilli Lateral Ventrikül Nodüllerinin Konvansiyonel ve Diffüzyon MR Görüntüleme Özellikleri

ÖZET

Amaç: Bu çalışmanın amacı halka şekilli lateral ventrikül nodüllerinin (RSLVN) konvansiyonel ve difüzyon MR bulgularını klinik özellikleriyle birlikte değerlendirmektir.

Gereç ve Yöntem: 2019-2023 yılları arasında kontrastlı beyin MR çekimi bulunan tüm hastaların MR görüntüleri retrospektif olarak değerlendirildi. T1 ağırlıklı (T1W), T2 ağırlıklı (T2W), FLAIR ve difüzyon ağırlıklı görüntülemede (DAG) RSLVN'lerin sayısı, şekli, maksimum çapı ve sinyal yoğunluğu ve kontrast tutulum durumu değerlendirildi. Nodüllerin görünür difüzyon katsayısı (ADC) değerleri ve normalleştirilmiş ADC oranları da belirlendi. Takip MR'ları yapıldıysa, RSLVN'lerin zaman içerisindeki morfolojik değişiklikleri değerlendirildi.

Bulgular: Çalışmaya dahil edilen 2920 hastanın 15'inde (%0,51) RSLVN saptandı. Beş hastada birden fazla RSLVN gözlendi ve dolayısıyla on beş hastada toplam 23 RSLVN tanımlandı. Nodüllerin sekizi (%34,8) lateral ventrikül tavanında, on iki tanesi (%52,2) ön boynuzda, üçü ise septum pellucidum'da yerleşmişti. 23 RSLVN'den 6'sı (%26,1) 1 cm'den büyüktü. Tüm RSLVN'ler T1W ve T2W'de izointens, FLAIR sekansında ise hiperintensti. DAG'de 23 RSLVN'den 20'sinde izointens sinyal vardı, geri kalan 3 lezyon ise hiperintens idi. Ortalama ADC değeri ve nADC oranı sırasıyla 1,42 ± 0,29 × 10-3mm2 ve 1,87 ± 0,31 idi.

Sonuç: RSLVN sıklığı daha önce bildirilenden daha sık olabilir. Konvansiyonel MR görünümleri ve tipik lokalizasyonları ayırt edicidir ve nispeten büyük boyutlara ulaşabilirler. Takip sırasındaki morfolojik stabilite ve bu lezyonların ADC değerleri olası benign bir doğaya işaret etmektedir.

Anahtar Kelimeler: RSLVN, Nörogörüntüleme, Manyetik Rezonans Görüntüleme, Nodül, Lateral Ventrikül.

INTRODUCTION

Ring-shaped lateral ventricular nodules (RSLVNs) are rare lesions attached to the ependyma located in the body or roof of the lateral ventricles. They are generally considered to be a "leave me alone" lesion not associated with clinical symptoms. However, the exact nature of RSLVNs is unknown due to the lack of adequate histopathological data (1,2). Some previous reports have suggested that RSLVNs may be a precursor or variant of subependymoma (3,4).

Various typical imaging findings of RSLVNs have previously been described on conventional brain MRI, including T1W, T2W, FLAIR, and contrast-enhanced sequences (1,2). However, the extremely rare prevalence of these lesions raises the question of the reliability of the available data. Moreover, to our best knowledge, the apparent diffusion coefficient (ADC) values of these lesions on diffusion MRI have not been measured before (1,2,5). The aim of this study was to evaluate the conventional brain MRI findings of RSLVNs and to assess the ADC values of these lesions along with signal intensity characteristics in diffusion MRI.

MATERIAL AND METHODS

Ethics Approval: This retrospective study was approved by our institutional ethics committee (Decision number: 826153) and carried out according to the requirements of the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study.

Patient Selection: The MR images of all patients who underwent contrast-enhanced cranial MRI in our institution between February 2019 and June 2023 were retrospectively evaluated. The exclusion criteria were: a) patients with cranial MRI examinations not suitable for evaluation due to motion or other artifacts; b) patients with collapsed lateral ventricles; c) known systemic or primary brain malignancy; d) history of brain radiotherapy or systemic chemotherapy.

MRI Protocol: MRI were performed using a 3 Tesla MR scanner (Ingenia; Philips Healthcare, Best, Netherlands). In all patients, the brain MRI protocol included the following sequences: sagittal turbo spin echo (TSE) T2, axial TSE T2 (repetition time (TR) 3,000 ms, echo time (TE) 80 ms, field-of-view (FOV) 185 mm × 230 mm, matrix size 400 × 320, slice thickness=5 mm), axial TSE T1 (TR 520 ms, TE 15 ms, FOV 256 mm × 256 mm, matrix size 400 × 320, slice thickness 5 mm), axial fluid attenuation inversion recovery (FLAIR) (TR 11,000 ms, TE 125 ms, inversion time 2500 ms, FOV 185 mm × 230 mm, matrix size 370 × 260, slice thickness=5 mm), axial single-shot echo-planar diffusion weighted imaging (DWI; TR 3200 ms, TE 80 ms, FOV 230 mm, matrix size 256 × 256, slice thickness = 5 mm, b value = 0-1000 mm^2/s) and pre- and post-contrast 3D T1 turbo fast echo (TFE) (TR/TE=26/6.2ms, FOV 24-26 cm, voxel size 1×1×1 mm^3, matrix=256 × 256, flip angle=25°). In addition, 3D Brain VIEW FLAIR sequence (TR 4800 ms, TE 351 ms, inversion time 1600 ms, FOV 20-24 cm, voxel size 1.5×1.5×1.5 mm^3, matrix size 216 × 180) was also available in some cases.

MRI Evaluation: MR images were reviewed by two experienced neuroradiologists (S.A and B.K., with 14 and 11 years of experience in neuroimaging, respectively) and any discrepancy resolved by consensus. MRI evaluation was performed using a dedicated PACS workstation (IntelliSpace Portal v7.0; Philips Healthcare, Best, Netherlands).

RSLVNs were diagnosed as ring-shaped nodular lesions attached to the lateral ventricular wall. Following the identification of each lesion, the number, location, shape and maximal axial diameter of the RSLVN were evaluated. In addition, the signal intensity of the ring portion of the nodules was assessed relative to the surrounding white matter, and the signal intensity of the core portion was assessed relative to the cerebrospinal fluid (CSF) on T1W, T2W and FLAIR images. Contrast enhancement characteristics of lesions were also evaluated.

On DWI, firstly, whether the RSLVN has diffusion restriction and its signal intensity characteristics (b1000) were visually evaluated. The ADC value was measured by placing a free-hand region of interest (ROI) of 5-40 mm^2 area in the ring portion of the lesion, avoiding the central core portion. Furthermore, normalized ADC (nADC) ratios are calculated as the ratio of the ADC in the tumor to the ADC in normal appearing contralateral white matter.

If follow-up MRI examinations were obtained, morphological changes of RLSVNs over time were evaluated.

Statistical Analysis: Statistical analyses were performed using SPSS version 21.0 software (SPSS Inc., Chicago IL, USA). Percentages (%) were used for categorical data and median values were used for continuous data in descriptive statistics.

RESULTS

A total of 2920 brain MRI examinations were evaluated and RSLVN was detected in 15 patients (0.51%). The mean age of 15 patients with RSLVN was 53.6 ± 16.07 (range 28-81) and 73.3% (n=11) of them were female. Brain MRI indications were headache in six patients, vertigo in two patients, screening for trauma in two patients, hemifacial spasm in one patient, meningioma follow-up in one patient, confusion in one patient, ICA aneurysm in one patient, and vertebral artery dissection in one patient.

Ten patients had a single RSLVN, while three patients had three and two patients had two.

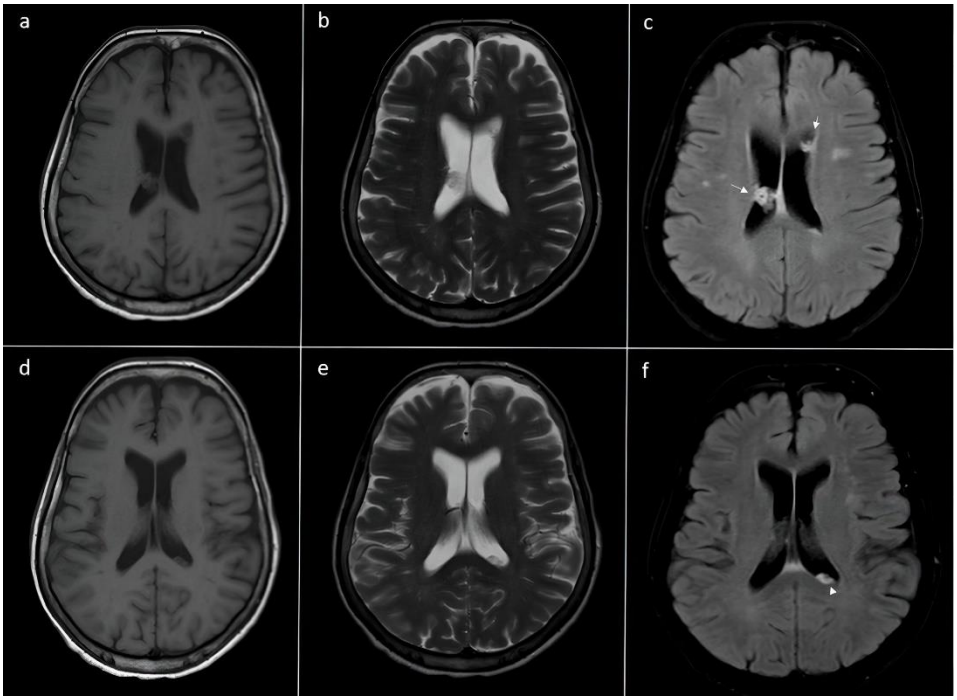

Figure 1. Three RSLVNs in different locations in a 71-year-old female patient (case 10). T1W (**a**), T2W (**b**) and FLAIR (**c**) images show two RSLVNs located in the body of the right lateral ventricle and the frontal horn of the left lateral ventricle, measuring 13mm and 9mm, respectively. In addition, T1W (**a**), T2W (**b**) and FLAIR (**c**) images of more inferior sections show another RSLVN in the left lateral ventricle. All identified RSLVNs have isointense signal on T1W and T2W and hyperintense signal on FLAIR

Therefore, a total of 23 RSLVNs were identified in fifteen patients. Nodules were located on the roof of the lateral ventricle body in eight nodules (34,8%), in the frontal horn in twelve nodules (52.2%), and in the septum pellucidum in three nodules (13%) (Figure 1). The mean maximum diameter of the RSLVNs was 7.73 mm (range 2-15 mm) and six nodules (26.1%) were larger than 1 cm. Of the 23 RSLVNs, 9 were lobular in shape, 8 were round, and 6 were oval.

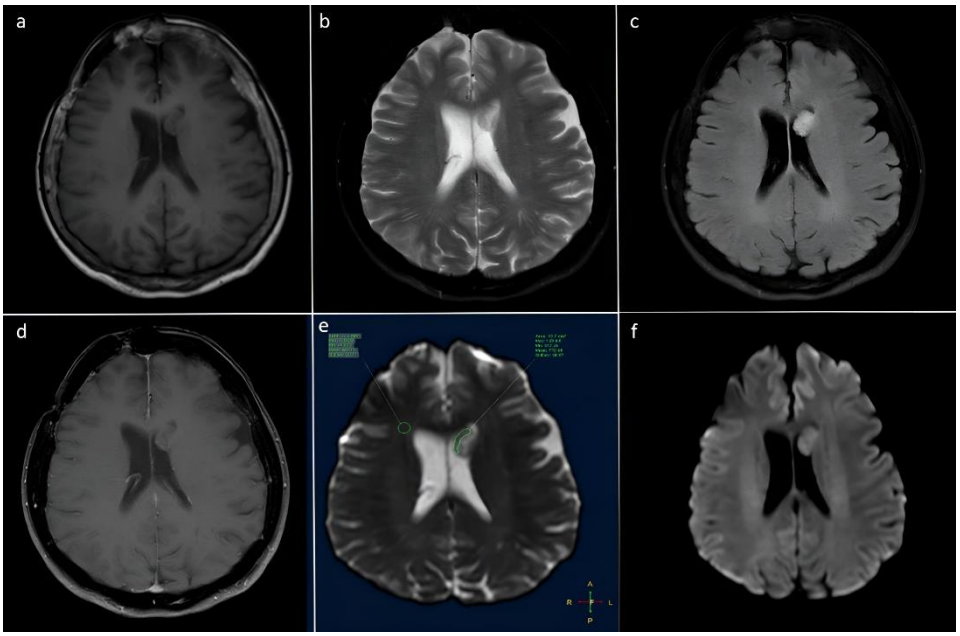

Figure 2. MRI findings of RSLVN located in the left frontal horn in a 63-year-old female patient (case 14). The peripheral portion of the lesion has hypointense signal on T1W (**a**) and T2W (**b**), hyperintense signal on FLAIR (**c**), and does not show enhancement on contrast-enhanced T1W image (**d**). On the other hand, the central portion of the lesion has the same intensity as the CSF on all sequences. **e** Measurement of ADC values of RSLVN and contralateral normal-appearing white matter is performed on grey-scale ADC images. **f** The lesion is slightly hyperintense on DWI (b1000)**.** This patient had previously undergone surgery due to sphenoid wing meningioma

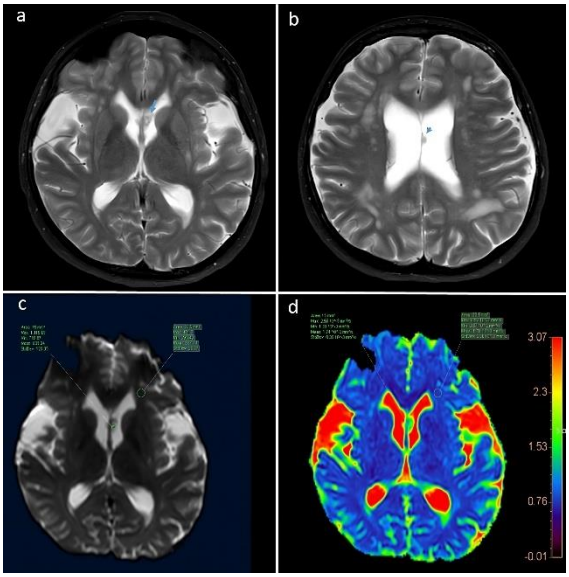

Figure 3. RSLVNs located in the septum pellicidum (case 8). **a,b** Axial T2-weighted images show two RSLVNs, 12 mm and 2 mm in size respectively, located in the septum pellicidum. **c,d** b0 DWI image and color ADC map of the 12 mm sized RSLVN, which is located more inferiorly. The mean ADC value of the lesion was measured as $1.74 \times 10^{-3} mm^2$

In all of the 23 RSLVNs, the signal intensity of the ring portion relative to the surrounding white matter, and the signal intensity of the core portion relative to CSF was isointense on T1- and T2-weighted imaging. On FLAIR imaging, all RSLVNs showed hyperintense signal. Contrast enhancement was not observed in any of the lesions on post-contrast T1-weighted imaging. On DWI, none of RSLVNs showed true diffusion restriction. 20 of 23 RSLVNs had isointense signal on DWI (b1000) compared to the adjacent brain parenchyma. On the other hand, the remaining 3 lesions were hyperintense on DWI (b1000) (Figure 2). The mean ADC of the 15 evaluated RSLVNs was $1.42 \pm 0.29 \times 10^{-3}$ mm^2/s, while the mean nADC ratio was 1.87 ± 0.31 (Figure 3).

No morphological changes were observed in any of the 16 RSLVNs in 12 patients with follow-up MRI at a median of 16.5 months. Detailed clinical and radiological findings are shown in Table 1.

DISCUSSION

In this study, we report the MRI and clinical findings of RSLVN in the largest population to date. Our study reveals that RSLVN is more common than previously reported. Shimono et al. reported the prevalence of RSLVN as 0.023%, while Nakajima et al. reported it as 0.45% (1,2). The higher prevalence in our study may be due to the higher awareness of RSLVN thanks to previous reports and the inclusion of lesions >1 cm. Various studies on RSLVNs have described them as nodular lesions commonly smaller than 1 cm (1,2,5,6). On the other hand, Pontillo et al. reported a giant RSLVN larger than 2.5 cm causing a mass effect and showed that these ring-shaped lesions can reach large sizes (3). In our study, six RSLVNs larger than 1 cm were observed, the largest of which was 15 mm in size.

Most of the cases diagnosed with RSLVN in the literature are middle-aged or older individuals, and it has been observed more frequently in male patients (1-6). In our study, RSLVN was also detected in middle-aged and older adults. However, most of our patients with RSLVN were female patients (73.3%). The roof of the body of the lateral ventricle or the frontal horn are reported as the typical locations of RSVLNs, as in most lesions in our study (1,2). On the other hand, for the first time, we observed RSLVNs located in the septum pellicidum in a patient.

The characteristic appearance of RSLVNs on conventional MR imaging is that the peripheral ring portion is isointense on T1W and T2W compared to the brain parenchyma and does not show contrast enhancement. On FLAIR imaging, although Shimono et al. identified two exceptionally isointense RSLVNs, the hyperintense signal is distinctive. In addition, the core portion of the RSLVN is expected to be isointense to CSF on T1WI, T2WI and FLAIR (1,2,5). Conventional MRI findings in our study confirmed these characteristic MRI features.

Previous studies and case reports have revealed that RSVLNs do not show diffusion restriction and have an isointense signal relative to the surrounding brain parenchyma on DWI (1-3). In our study, none of the RSLVNs showed diffusion restriction and the vast majority of them were isointense on DWI. However, unlike previous studies, 13% (n = 3) of the RLSVNs had hyperintense signal on DWI. In addition, we measured the ADC values (absolute ADC and nADC ratio) of RSLVNs for the first time. These ADC values of RSLVNs can provide information about the possible nature of these nodules and serve as a reference for future studies. ADC values are a major determinant of tumor cellularity in brain tumors, and high ADC values are associated with low cellularity. For gliomas and meningiomas, absolute ADC values above $0.8\text{-}1 \times 10^{-3}$ mm^2/s generally indicate low cellularity and low-grade tumor (7,8). Moreover, since the absolute ADC values in benign tumors are usually higher than the normal-appearing white matter, the nADC ratios in these tumors are above 0.99 (9). Therefore, the high ADC values and nADC ratios of RSLVNs in our study support that these lesions are probably of a benign nature.

Although the exact nature of RSLVNs is unknown due to inadequate histopathological data, five different possibilities have been hypothesized: a) neuroglial or glioependymal cyst; (b) inflammatory nodular formation of ependyma

Table 1. Magnetic resonance imaging and clinical features of patients diagnosed with RSLVN

Case	Age/Sex	Location	Shape /Diameter	Signal intensity on T1WI	Signal intensity on T2WI	Signal intensity on FLAIR	Signal intensity on DWI	ADC value	NADC ratio	Contrast enhancement	Follow-up period
1	38/M	Right frontal horn	Oval/4 mm	Isointense	Isointense	Hyperintense	Isointense	1.22	1.67	None	N/A
		Left frontal horn	Round/3mm	Isointense	Isointense	Hyperintense	Isointense	N/A	N/A	None	
		Roof of left body	Round/3mm	Isointense	Isointense	Hyperintense	Isointense	N/A	N/A	None	
2	46/F	Right frontal horn	Oval/ 11mm	Isointense	Isointense	Hyperintense	Isointense	1.02	1.54	None	4 months
3	43/F	Right frontal horn	Lobular/14mm	Isointense	Isointense	Hyperintense	Isointense	1.42	1.91	None	8 months
4	76/F	Roof of left body	Round/5mm	Isointense	Isointense	Hyperintense	Isointense	1.46	1.71	None	50 months
		Right frontal horn	Round/4mm	Isointense	Isointense	Hyperintense	Isointense	N/A	N/A	None	
5	81/F	Roof of right body	Lobular/ 9mm	Isointense	Isointense	Hyperintense	Isointense	1.75	2.36	None	37 months
6	40/F	Roof of right body	Lobular/ 9mm	Isointense	Isointense	Hyperintense	Isointense	1.20	1.73	None	5 months
7	66/M	Right frontal horn	Oval/ 6mm	Isointense	Isointense	Hyperintense	Isointense	1.98	2.4	None	5 months
8	28/F	Septum pellucidum	Oval/12mm	Isointense	Isointense	Hyperintense	Isointense	1.81	2.38	None	N/A
		Septum pellucidum	Round/3mm	Isointense	Isointense	Hyperintense	Isointense	N/A	N/A	None	
		Septum pellucidum	Round/2mm	Isointense	Isointense	Hyperintense	Isointense	N/A	N/A	None	
9	51/M	Roof of left body	Round/ 5mm	Isointense	Isointense	Hyperintense	Isointense	1.21	1.77	None	N/A
10	71/F	Roof right body	Lobular/13mm	Isointense	Isointense	Hyperintense	Isointense	1.80	2.19	None	12 months
		Left frontal horn	Lobular/ 9mm	Isointense	Isointense	Hyperintense	Isointense	N/A	N/A	None	
		Roof of left body	Lobular/ 7mm	Isointense	Isointense	Hyperintense	Isointense	N/A	N/A	None	
11	41/F	Right frontal horn	Lobular/11mm	Isointense	Isointense	Hyperintense	Hyper-intense	1.56	1.91	None	16 months
12	56/M	Left frontal horn	Lobular/11mm	Isointense	Isointense	Hyperintense	Isointense	1.55	2,03	None	18 months
13	70/F	Right frontal horn	Oval/ 8mm	Isointense	Isointense	Hyperintense	Isointense	1.12	1.47	None	52 months
		Left frontal horn	Round/5mm	Isointense	Isointense	Hyperintense	Isointense	N/A	N/A	None	
14	63/F	Left frontal horn	Lobular/15mm	Isointense	Isointense	Hyperintense	Hyper-intense	1.24	1.58	None	17 months
15	34/F	Roof of left body	Oval/9mm	Isointense	Isointense	Hyperintense	Hyper-intense	1.1	1.54	None	24 months

similar to granuloma; (c) astrocytic gliosis reactive to adjacent subependymal veins; (d) redetachment of the fused portion of coarctation of the ventricle frontal horns; (e) variety of subependymoma (1). The most prominent among these is subependymoma. Because two recent reports revealed the histopathological diagnosis of RLSVNs as subpendymoma (3,4). Moreover, subependymomas located in the lateral ventricle may have various clinical and radiological features resembling RSLVNs. Subependymomas are intraventricular, usually smaller than 2 cm, lobular, well-circumscribed, non-enhancing tumors on MRI, which are usually detected incidentally in middle-aged and elderly adults (10,11). They may be localized in the body of the lateral ventricle, the frontal horn, or the septum pellucidum and have a ring-shaped appearance (3,12). These features are also commonly observed in RSLVNs in the literature and in our study (1,2,6). Additionally, subependymomas can be multiple, like RSLVNs (11).

The morphological stability of RSLVNs over time and their lack of association with clinical symptoms emphasize the possible benign nature of these lesions. Thus, the optimal management recommended for RSLVNs with typical clinical and radiological features is periodic follow-up (5).

Limitations: The main limitations of our study were the retrospective design and relatively small sample size. In addition, ADC measurements was not performed in some lesions due to small lesion size. Finally, none of the identified RSLVNs had a histopathological diagnosis.

CONCLUSION

Our study is the largest experience reported in the literature to date regarding the MRI and clinical characteristics of RSLVNs. These lesions may be more common than previously reported and can reach sizes greater than 1 cm. Their distinctive MRI appearances and typical localizations (body of the lateral ventricle, frontal horn and septum pellucidum) are helpful in making the diagnosis. The absence of association with symptoms, morphological stability during the follow-up interval and high ADC values suggest a possible benign nature.

Declarations:

Funding: No funding was received for conducting this study.

Compliance with Ethical Standards

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul University-Cerrahpasa.

Conflicts of Interest: The authors have no relevant financial or non-financial interests to disclose.

Informed Consent: Informed consent was waived because of the retrospective nature of the study.

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RESEARCH ARTICLE

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Exploring Perspectives on Cancer Screening in People Aged 30-70: A Comparative Study of Those with and Without Type 2 Diabetes

ABSTRACT

Objective: The aim of the study was to assess attitudes and behaviors related to cancer screening using an attitude scale for cancer screening among individuals aged 30-70 with and without type 2 diabetes mellitus.

Materials and Methods: This prospective case-control study was conducted from March to May 2023 at a single center. A total of 197 participants, including 67 patients with type 2 diabetes mellitus and 130 participants without type 2 diabetes mellitus aged 30-70, were enrolled using simple random sampling. For the assessment, a sociodemographic form prepared through a literature review and the attitude scale for cancer screening were used. A statistical significance level of $p<0.05$ was considered.

Results: The study participants had an average age of 49.65±12.49 years. The attitude scale for cancer screening scores did not show a statistically significant difference between individuals with and without type 2 diabetes mellitus ($z=1.485$, $p=0.138$). Furthermore, the statistical analysis did not identify a significant difference with the total score of the attitude scale for cancer screenings among other variables. Positive correlation was found between the attitude scale for cancer screening total score and age (rho= 0.206, $p=0.004$).

Conclusions: In our study, statistically significant differences in attitudes and behaviors towards cancer screenings were not observed between individuals with and without type 2 diabetes mellitus. However, it is essential to be attentive to the elevated risk of cancer in patients with type 2 diabetes mellitus. Therefore, increasing awareness and screening rates for cancer in this group is crucial.

Keywords: Diabetes Mellitus Type 2, Diagnosis, Early Detection of Cancer, Hyperglycemia.

30-70 Yaş Aralığındaki Kişilerde Kanser Taraması Perspektiflerinin İncelenmesi: Tip 2 Diyabeti Olanlar ve Olmayanların Karşılaştırmalı Bir Çalışması

ÖZET

Amaç: Çalışmada tip 2 diyabetes mellitusu olan ve olmayan 30-70 yaş arası kişiler arasında kanser taramalarına yönelik tutum ölçeği kullanarak kanser taramalarına yönelik tutum ve davranışların değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Prospektif vaka-kontrol tipte çalışma, Mart-Mayıs 2023 tarihleri arasında tek merkezde gerçekleştirilmiştir. 30-70 yaş aralığında tip 2 diyabetes mellitusu olan 67 hasta ve tip 2 diyabetes mellitusu olmayan 130 katılımcı olmak üzere toplamda 197 katılımcı, basit rastgele örnekleme yöntemiyle seçilmiştir. Değerlendirmenin yapılması amacıyla, literatür taraması yoluyla hazırlanan sosyodemografik form ve 'kanser taramalarına yönelik tutum ölçeği' kullanılmıştır. İstatistiksel anlamlılık düzeyi $p<0.05$ olarak kabul edilmiştir.

Bulgular: Çalışmaya katılan bireylerin yaş ortalaması 49.65±12.49 yıl olarak elde edilmiştir. Tip 2 diyabetes mellitus tanısı olan ve olmayan kişiler arasında kanser taramalarına yönelik tutum ölçeği puanları açısından istatistiksel olarak anlamlı bir fark yoktur ($z=1.485$, $p=0.138$). Diğer değişkenlerin de kanser taramalarına yönelik tutum ölçeği toplam puanıyla istatistiksel olarak anlamlı bir fark tespit edilmemiştir. Kanser taramalarına yönelik tutum ölçeği toplam puanı ile yaş arasında pozitif yönlü istatistiksel olarak anlamlı bir ilişki bulunmaktadır (rho= 0.206, $p=0.004$).

Sonuç: Çalışmamızda, tip 2 diyabetes mellitusu olan ve olmayan bireyler arasında kanser taramalarına yönelik tutum ve davranışlarında istatistiksel olarak anlamlı fark tespit edilmemiştir. Ancak, tip 2 diyabetes mellitus hastalarında kanser riskinin yüksekliğine dikkat etmek gereklidir. Bu nedenle, bu grupta kanser taramalarına yönelik farkındalığı artırmak ve tarama oranlarını yükseltmek önemlidir.

Anahtar Kelimeler: Diyabetes Mellitus Tip 2, Tanı, Kanserin Erken Tespiti, Hiperglisemi.

INTRODUCTION

Cancer and diabetes are two of the most significant global health challenges, leading to substantial mortality and morbidity (1). Epidemiological studies indicate that individuals with diabetes have a considerably higher risk of various cancers, including stomach, breast, and cervical cancers (2–5). Although not all aspects of the relationship between diabetes and cancer are fully understood, the most likely mechanisms involve insulin resistance and hyperinsulinemia. Given the higher incidence of cancer in individuals with diabetes, it may be reasonable to consider initiating screenings, especially for malignancies like breast, colon, and endometrial cancer, earlier than in healthy individuals, even though the benefits are not definitively established (6).

Cancer screenings are conducted to achieve the early detection of cancer or its precursor lesions in asymptomatic individuals. The primary goal is to reduce the morbidity and mortality associated with cancer (7). In Turkey, screening is conducted within national breast, cervical, and colorectal cancer standards. In this context, screening is carried out for breast cancer in women aged 40-69, cervical cancer in women aged 30-65, and colorectal cancer in individuals aged 50-70 (8). The significance of cancer screening and early diagnosis is particularly pronounced for individuals with diabetes. Given the relatively higher healthcare needs and the number of visits to the healthcare system by patients with type 2 diabetes mellitus (T2DM), it is reasonable to assume that their attitudes, behaviors, and awareness regarding cancer screenings may be higher than those without T2DM. In the conducted literature review, studies examining the relationship between attitudes and behaviors towards chronic diseases and cancer screenings have been identified. However, specifically, no studies investigating attitudes and behaviors towards cancer screenings in individuals with diabetes mellitus were found.

This study aims to assess the attitudes and behaviors towards cancer screenings in individuals aged 30-70 with and without T2DM.

MATERIAL AND METHODS

A single-center prospective case-control study was conducted between March 6, 2023, and May 6, 2023, with patients who presented to the Family Medicine Polyclinic and Family Medicine Clinic Diabetes Polyclinic at a training and research hospital, and were either diagnosed with or without T2DM. The study obtained medical ethics committee approval on February 6, 2023, under decision number 2023/23-4062.

In Turkey, within the scope of the national cancer screening program, individuals aged 30-70 undergo cancer screening. From the pool of 400 patient applications within the age range of 30-70, the minimum required sample size for the study was 197 individuals. Upon stratification, this number was further divided into a minimum of 67 patients with a T2DM diagnosis and 130 individuals without a T2DM diagnosis. Patients with any mental or psychological disorders, as well as those who have recovered from cancer or currently have active cancer, were not included in the study. Patients were selected through a simple random sampling method and subsequently categorized into two groups: those with a T2DM diagnosis and those without. The patients signed informed consent forms based on voluntariness after face-to-face meetings. A data collection form was completed, which included questions related to age, gender, educational background, duration of education, presence of T2DM, additional chronic illnesses, and smoking status. The Attitude Scale for Cancer Screening (ASFCS) was then administered. All procedures performed in studies involving human participants were by the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

ASFCS is a single-dimensional, 24-item scale developed by Öztürk and colleagues in 2019. It has undergone validation and reliability studies in the Turkish context. The scale uses a five-point Likert type format, with the following response options: '1: Strongly Disagree, 2: Disagree Somewhat, 3: Neither Agree nor Disagree, 4: Agree Somewhat, 5: Strongly Agree.' ASFCS does not have specific cut-off points. Participant scores approaching 24 indicate a negative attitude towards cancer screening, while scores nearing 120 suggest a positive attitude towards cancer screening (9).

Statistical Analysis: Demographic information, such as gender, educational background, smoking status, and the presence of chronic illnesses, was represented using number (n) and percentage (%) values to show the distribution of responses.

For continuous variables in the study, like age and ASFCS scores, their suitability for a normal distribution was assessed both graphically and through the Shapiro-Wilks test. It was determined that none of the continuous variables followed a normal distribution. Therefore, in the presentation of descriptive statistics, median (IQR-Interquartile Range) values were used.

In the comparison of individuals' ASFCS scores based on categorical variables with more than two categories, such as educational background and smoking status, the Kruskal-Wallis test was employed. For pairwise comparisons, the Mann-Whitney U non-parametric variance analysis was used.

In a model constructed based on variables like gender, educational background, duration of education, T2DM diagnosis, hypertension, cardiovascular disease, hyperlipidemia,

hypothyroidism, and asthma or chronic obstructive pulmonary disease (COPD) status, the ASFCS score didn't exhibit a normal distribution. Therefore, generalized linear models (GLM) were utilized.

Statistical analyses and calculations were conducted using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs. The statistical significance level was set at $p<0.05$.

RESULTS

The study revealed that the participants had an average age of 49.65±12.49 years, ranging from a minimum of 30.0 years to a maximum of 70.0 years. In diabetic patients, the average duration of diabetes was 9.82±5.92 years. Moreover, the mean total ASFCS score was 104.36±10.64. Notably, there was no statistically significant difference in ASFCS scores between individuals with and without T2DM (z=1.485, p=0.138). A weak, positive, and statistically significant relationship was identified between the ASFCS total score and age (rho: 0.206, p: 0.004). Importantly, this relationship was observed in patients without T2DM (rho: 0.256, p: 0.003) but not in those with T2DM (rho: -0.015, p: 0.903). Additionally, no statistically significant relationship was found between the ASFCS total score and the duration of diabetes (rho: 0.098, p: 0.432).

The study revealed no statistically significant differences in ASFCS scores between individuals with and without T2DM across all variable groups (p>0.05) (Table 1).

Table 1. Comparison of Demographic Characteristics and Attitude Scale for Cancer Screening Total Scores of Participants in Independent Variable Groups

		T2DM Diagnosed				T2DM Not Diagnosed			
			Test Statistic*				Test Statistic*		
		n (%)	Median (IQR)	Z ; $\chi 2$	p	n (%)	Median (IQR)	Z ; $\chi 2$	p
Gender	Female	35 (52.2)	108.0 (17.0)	z=0.710	0.478	81 (62.3)	104.0 (12.0)	z=0.613	0.540
	Male	32 (47.8)	109.5 (11.0)			49 (37.7)	105.0 (19.0)		
Education Level	Illiterate	3 (4.5)	101.0 (N/A)	$\chi 2$=4.563	0.471	2 (1.5)	101.0 (N/A)	$\chi 2$=5.300	0.380
	Primary School	25 (37.3)	107.0 (18.0)			19 (14.6)	111.0 (11.0)		
	Elementary School	8 (11.9)	110.5 (14.0)			8 (6.2)	104.5 (14.0)		
	High School	14 (20.9)	111.5 (11.0)			38 (29.3)	106.0 (13.0)		
	College	5 (7.5)	111.0 (20.0)			6 (4.6)	95.5 (29.0)		
	University	12 (17.9)	109.0 (17.0)			57 (43.8)	103.0 (12.0)		
Education Duration	12 years or less	50 (74.6)	108.5 (17.0)	z=0.195	0.846	67 (51.5)	107.0 (13.0)	z=1.452	0.146
	More than 12 years	17 (25.4)	109.0 (16.0)			63 (48.5)	103.0 (13.0)		
Hypertension	Absent	26 (38.8)	108.0 (18.0)	z=0.754	0.451	112 (86.2)	104.0 (14.0)	z=0.954	0.340
	Present	41 (61.2)	110.0 (15.0)			18 (13.8)	108.0 (12.0)		
Cardiovascular Disease	Absent	51 (76.1)	109.0 (18.0)	z=1.590	0.112	120 (92.3)	104.0 (14.0)	z=1.805	0.071
	Present	16 (23.9)	105.0 (14.0)			10 (7.7)	110.0 (15.0)		
Hyperlipidemia	Absent	50 (74.6)	108.5 (21.0)	z=1.132	0.257	123 (94.6)	104.0 (13.0)	z=0.996	0.319
	Present	17 (25.4)	110.0 (7.0)			7 (5.4)	108.0 (13.0)		
Hypothyroidism or Hyperthyroidism	Absent	59 (88.1)	109.0 (14.0)	z=0.019	0.985	121 (93.1)	105.0 (15.0)	z=0.427	0.670
	Present	8 (11.9)	108.0 (24.0)			9 (6.9)	102.0 (5.0)		
Asthma or COPD	Absent	62 (92.5)	109.0 (15.0)	z=0.406	0.702	128 (98.5)	105.0 (14.0)	z=0.454	0.650
	Present	5 (7.5)	109.0 (23.0)			2 (1.5)	100.5 (N/A)		
Other Diseases	Absent	59 (88.1)	108.0 (17.0)	z=1.704	0.088	126 (96.9)	105.0 (14.0)	z=0.128	0.898
	Present	8 (11.9)	113.0 (10.0)			4 (3.1)	103.5 (33.0)		
Smoking Use	No	41 (61.2)	108.0 (19.0)	$\chi 2$=2.995	0.224	70 (53.8)	105.0 (13.0)	$\chi 2$=4.645	0.098
	Yes	14 (20.9)	110.0 (14.0)			44 (33.8)	107.0 (12.0)		
	Quit	12 (17.9)	105.5 (17.0)			16 (12.4)	98.0 (15.0)		

z=Mann Whitney U Test Statistics, χ^2=Kruskal Wallis Test Statistics, N/A: Not Available

The results of the generalized linear model (GLM) established with the ASFCS total score as the dependent variable and independent variables such as gender, educational background (below high school, high school and above), duration of education, T2DM diagnosis, hypertension, cardiovascular disease, hyperlipidemia, hypothyroidism, asthma or COPD, and other chronic illnesses are presented in Table 2.

The table includes the coefficients of the parameters, standard error values, and p-values. In the established model, the variable "hyperlipidemia" has a statistically significant contribution (p=0.014).

Table 2. Generalized Linear Model for Predicting the Attitude Scale for Cancer Screening

	B Coefficient	Std. Error	p
Constant	102.711	1.846	**<0.001**
Gender	-1.216	1.548	0.432
Education Level	2.614	2.035	0.199
Education Duration	-2.100	1.866	0.260
T2DM Diagnosis	-0.189	1.860	0.919
Hypertension	1.684	2.045	0.410
Cardiovascular Disease	-3.467	2.979	0.245
Hyperlipidemia	7.321	2.975	**0.014**
Hypothyroidism or Hyperthyroidism	1.757	2.826	0.534
Asthma or COPD	-0.140	4.140	0.973
Other Chronic Diseases	3.780	3.160	0.232

DISCUSSION

In our study, no statistically significant differences were found in ASFCS scores across groups of individuals with and without T2DM concerning variables such as gender, educational level and duration, the presence of chronic illnesses, and smoking.

In a study conducted by Öztürk et al. in 2019, it was observed that as age increased, attitudes towards cancer screenings became more positive (9). Sevinç et al. showed in their study that as age increases, the recognition of cancer screening tests also increases (10). Similarly, a study by Tekpınar et al. in 2017 indicated that as age increased, attitudes towards cancer screenings became more favorable (11). However, a different perspective was presented by Onitilo et al. in their study on the relationship between diabetes and cancer. They found that younger individuals with higher education levels had a higher rate of undergoing mammography screenings and exhibited more positive behaviors towards cancer screenings (12). Furthermore, in a study conducted by McBean et al. in 2007, it was noted that diabetic women used screening services less as they grew older (13). In our study, a statistically significant positive relationship between age and ASFCS scores was found among individuals without T2DM. This suggests the need for greater awareness and education about the importance of cancer screenings and preventive healthcare among younger individuals.

Bynum et al. conducted a study in the United States, which revealed that individuals with lower levels of education were less likely to undergo cancer screenings. This observation led to the suggestion that participants' reluctance might stem from a lack of belief in the life-saving benefits of these screenings (14). In a study where 79% of the participants had received education below the high school level, it was observed that the level of knowledge and awareness about cancer types, screening methods, and screening programs was quite low (15). In 2008, Zhao et al. reported an increased rate of mammography, cervical, and colorectal cancer screenings with higher levels of education (16). Conversely, a 2017 study by Tekpınar and colleagues found that as education levels increased, attitudes toward cancer screenings became more negative (11). Additionally, a 2016 study by Wools and associates noted that lower education levels were associated with higher participation in cancer screenings (17). However, in our study, no statistically significant difference was observed between education levels and ASFCS scores. This lack of difference may be attributed to the accessibility and recommendation of cancer screenings in primary healthcare centers, irrespective of individuals' educational backgrounds.

Suh et al. conducted a study and found that cancer screening rates among diabetic individuals were significantly lower than those of non-diabetic individuals, emphasizing the need for recommended cancer screenings suitable for age and gender for all diabetic patients to support primary prevention and early diagnosis (18). Onitilo et al. reported in their study that diabetic women had lower rates of clinical breast examination, pap smears, breast self-examination, and breast skin checks compared to non-diabetic women, and that colorectal cancer screening rates were lower in diabetics compared to non-diabetics. The exact reasons for lower cancer screening rates in diabetic patients were noted to be not fully clear (12). Limpscombe et al. also conducted a study in which they noted that diabetic women, despite having more visits to primary care physicians and specialist consultations, had a significantly lower probability of getting a mammogram within a 2-year period compared to non-diabetic women. The study suggested that the presence of diabetes posed a barrier to regular mammography screenings and that in patients with chronic conditions, preventive care might be relatively neglected. It was further stated that as the complexity of diabetes care increased, developing more standardized strategies would be crucial to ensure the continuity of comprehensive care (19). In a study by McDaniel et al. in the United States in 2021, examining the rates of HPV testing among women with and without diabetes, it was noted that even after adjustments for other factors, diabetic women had lower rates of undergoing HPV tests compared to non-diabetic women (20).

Miller et al. reported in their study that overall adherence to cervical cancer screening was lower in diabetic women compared to non-diabetic women, but emphasized that this might not be primarily due to diabetes but could be attributed to differences in sociodemographic characteristics and access to healthcare services. It was also pointed out that due to lower cervical cancer survival in diabetic women and the increasing prevalence of diabetes, cervical cancer screening should be increased in this population (21).

In the studies we reviewed, it is generally observed that individuals with diabetes exhibit less favorable behaviors related to cancer screenings, and their screening rates are lower compared to those without diabetes. In our study, when we compared individuals with and without T2DM based on their ASFCS total scores, no statistically significant difference was found in terms of attitudes and behaviors related to cancer screenings. Given that some cancer types have a higher incidence in individuals with T2DM, efforts can be made to increase awareness of cancer screenings. Providing the necessary information and guidance

regarding cancer screenings can contribute to improving screening rates and awareness.

Among the participants in our study, 29.4% reported being smokers, 14.2% had quit smoking, and 56.4% were non-smokers. A study by Jimenez-Garcia and colleagues found that smoking was significantly less prevalent among diabetic women compared to non-diabetic women (22). In the study conducted by Öztürk et al., it was noted that individuals who smoke exhibited a more positive attitude towards cancer screenings (9). However, in our study, it was observed that the ASFCS scores of individuals who smoked were higher than those who didn't, but this difference was not statistically significant.

Yegenler et al. found that the presence of a chronic illness was a factor that positively affected the attitude toward cancer screening (23). In contrast, a study conducted by Erkal in 2022 found no significant difference in attitudes towards cancer screenings in relation to the presence of chronic diseases, similar to our study (24). Öztürk et al.'s study also did not reveal a significant relationship between the presence of chronic diseases and attitudes towards cancer screenings (9). In our study, no statistically significant difference was found in the relationship between the presence of chronic diseases and ASFCS scale scores. However, according to the generalized linear model established in our study, only hyperlipidemia contributes statistically significantly to the model. The reason for the lack of a relationship between the presence of chronic diseases in our study and attitudes and behaviors towards cancer screenings may be explained by the psychological impact on individuals with chronic diseases. They may avoid cancer screenings out of fear of being diagnosed with serious and life-threatening illnesses such as cancer.

The study we conducted is a single-center study, and due to the fact that the participants consisted of individuals seeking care at a tertiary healthcare institution, the results may not reflect the general population. This circumstance can be considered a limitation of our study. Additionally, the low sample size can be regarded as another constraint.

In conclusion, although it is established that certain cancers are more prevalent in diabetic patients, our study did not reveal a statistically significant difference in attitudes and behaviors toward cancer screenings between individuals with and without T2DM. However, considering the higher cancer risk in diabetic patients, increasing awareness and improving cancer screening rates among these patients is necessary and important. In our study, it was observed that as age increased, patients had a more positive attitude and behavior towards cancer screenings. However, this relationship was not observed in diabetic patients. Therefore, it is recommended that all healthcare professionals, especially primary care physicians, provide more information and guidance about cancer screenings in diabetic patients. Conducting studies to improve cancer attitudes and behaviors, particularly among younger individuals and newly diagnosed T2DM patients, may be appropriate.

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RESEARCH ARTICLE

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Mean Platelet Volume (MPV) in Obstructive Sleep Apnea (OSA) and Effect of Continuous Positive Airway Pressure (CPAP) Treatment on MPV in OSA

ABSTRACT

Objective: In this study, our objective was to evaluate mean platelet volume (MPV), an indirect marker of platelet activation, in patients with obstructive sleep apnea (OSA), and assess the effect of OSA treatment with continuous positive airway pressure (CPAP) on MPV.

Materials and Methods: In this study, records of consecutive patients who underwent polysomnographic evaluation for OSA symptoms in the Sleep Disorders Laboratory during a one-year period were reviewed retrospectively. Patients who had both complete blood count and MPV measurements were included in the study.

Results: A total of 158 patients, including 51 females (32.3%) and 107 males (67.7%), were included in the study. The mean age of the patients was 51±13 (min-18, max-82) years. OSA was detected in 74.1% (117/158) of the patients. It was determined that as the severity of OSA increased, hemoglobin and hematocrit values increased significantly. There was no significant difference in platelet count according to the presence and severity of OSA. The MPV was significantly lower in severe OSA cases compared to those without OSA and mild OSA cases. A negative correlation was observed between MPV and the apnea-hypopnea index, desaturation index, and the amount of oxygen saturation below 90% during sleep. There was no significant difference in median erythrocyte and thrombocyte counts, hematocrit percentage and hemoglobin values before and after treatment in OSA patients who used CPAP therapy. However, a significant decrease in MPV was observed after OSA treatment compared to pre-treatment. (p=0.021).

Conclusions: The results of the study do not support an increase in MPV and hence platelet activation in severe OSA patients compared with those without OSA. However, the results suggest that one month of CPAP treatment reduces MPV and thus platelet activation in severe OSA patients. Further controlled, prospective studies including treatment outcomes are needed on this subject.

Keywords: Sleep Apnea, Mean Platelet Volume, Obstructive Sleep Apnea, Platelets.

Obstrüktif Uyku Apnede (OUA) Ortalama Trombosit Hacmi (OTH) ve OUA'da Sürekli Pozitif Hava Yolu Basıncı (CPAP) Tedavisinin OTH Üzerine Etkisi

ÖZET

Amaç: Bu çalışmada amacımız, obstrüktif uyku apnesi (OUA) olan hastalarda trombosit aktivasyonunun dolaylı bir belirteci olan ortalama trombosit hacmini (OTH) değerlendirmek ve sürekli pozitif hava yolu basıncı (CPAP) ile OUA tedavisinin OTH üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Bu çalışmada, Uyku Bozuklukları Laboratuvarı'nda bir yıl boyunca OSA semptomları nedeniyle polisomnografik değerlendirme yapılan ardışık hastaların kayıtları retrospektif olarak incelendi. Çalışmaya hem tam kan sayımı hem de MPV ölçümü yapılan hastalar dahil edildi.

Bulgular: Çalışmaya 51 kadın (%32.3) ve 107 erkek (%67.7) olmak üzere toplam 158 hasta dahil edildi. Hastaların yaş ortalaması 51±13 (min-18, maks-82) yıldı. Hastaların %74,1'inde (117/158) OSA saptandı. OSA şiddeti arttıkça hemoglobin ve hematokrit değerlerinin anlamlı olarak arttığı belirlendi. Trombosit sayısında OSA varlığı ve şiddetine göre anlamlı bir fark yoktu. MPV, ağır OSA olgularında OSA olmayanlara ve hafif OSA olgularına kıyasla anlamlı derecede düşüktü. OTH ile apne-hipopne indeksi, desatürasyon indeksi ve uyku sırasında %90'ın altındaki oksijen satürasyonu miktarı arasında negatif bir korelasyon gözlendi. CPAP tedavisi kullanan OSA hastalarında tedavi öncesi ve sonrası medyan eritrosit ve trombosit sayıları, hematokrit yüzdesi ve hemoglobin değerlerinde anlamlı bir fark bulunmadı. Bununla birlikte, OSA tedavisi sonrasında tedavi öncesine kıyasla MPV'de anlamlı bir düşüş gözlendi. (p=0.021).

Bulgular: Çalışmaya dahil edilen 2920 hastanın 15'inde (%0,51) RSLVN saptandı. Beş hastada birden fazla RSLVN gözlendi ve dolayısıyla on beş hastada toplam 23 RSLVN tanımlandı. Nodüllerin sekizi (%34,8) lateral ventrikül tavanında, on iki tanesi (%52,2) ön boynuzda, üçü ise septum pellucidum'da yerleşmişti. 23 RSLVN'den 6'sı (%26,1) 1 cm'den büyüktü. Tüm RSLVN'ler T1W ve T2W'de izointens, FLAIR sekansında ise hiperintensti. DAG'de 23 RSLVN'den 20'sinde izointens sinyal vardı, geri kalan 3 lezyon ise hiperintens idi. Ortalama ADC değeri ve nADC oranı sırasıyla 1,42 ± 0,29 × 10-3mm2 ve 1,87 ± 0,31 idi.

Sonuç: Çalışmanın sonuçları, OSA'sı olmayanlara kıyasla ağır OSA hastalarında MPV'de ve dolayısıyla trombosit aktivasyonunda bir artışı desteklememektedir. Ancak, sonuçlar bir aylık CPAP tedavisinin ağır OUA hastalarında MPV'yi ve dolayısıyla trombosit aktivasyonunu azalttığını düşündürmektedir. Bu konuda tedavi sonuçlarını içeren daha ileri kontrollü, prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Uyku Apne, Ortalama Trombosit Hacmi, Obstruktif Uyku Apne, Trombositler.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common worldwide condition, estimated to affect approximately 1 billion people globally, with a prevalence exceeding 50% in some countries (1-3).

Cardiovascular complications are the most significant issues associated with OSA (4-8). The development of cardiovascular diseases in OSA involves a multifactorial process, including fluctuations in negative intrathoracic pressure, intermittent hypoxia and hypercapnia, increased sympathetic nervous system activity, vascular endothelial dysfunction, oxidative stress, systemic inflammation, excessive platelet activation, and metabolic dysregulation (5).

Epidemiological data support the notion that OSA is an independent risk factor for cardiovascular diseases. These observations have prompted research into the role of OSA in the pathogenesis of cardiovascular diseases. Platelets play a key role in cardiovascular diseases, and increased platelet activation is suggested to be a significant contributor to the frequent cardiovascular complications in OSA patients (9). Mean platelet volume (MPV) is a parameter that reflects platelet function and activity (10). Increased MPV indicates larger platelet size (11). Larger platelets are metabolically more active and more prone to adhesion and aggregation compared to smaller platelets (10, 12). They contain more alpha granules and platelet-derived substances. The increased activity of larger platelets may be attributed to higher thromboxane A2 production compared to smaller platelets (10). Increased platelet volume is associated with indicators of platelet activation, including increased aggregation, TxA2 synthesis, serotonin levels, release of platelet factor-4 and β-thromboglobulin, and expression of adhesion molecules (13,14). MPV, measured as part of a complete blood count, can safely estimate potential platelet activity and aggregation (10, 15).

In this study, our objective was to evaluate MPV, an indirect marker of platelet activation, in OSA patients, and assess the effect of OSA treatment with continuous positive airway pressure (CPAP) on MPV.

MATERIAL AND METHODS

Study Population: In this study, we retrospectively analyzed the records of consecutive patients admitted to the Sleep Respiratory Disorders Laboratory of the Chest Diseases Clinic of Duzce University Faculty of Medicine within one year (2012) with OSA symptoms. Consecutive patients who underwent a complete polysomnography test with both complete blood count (CBC) and mean platelet volume (MPV) measurements were included in the study. The study was approved by the Non-Invasive Clinical Research Ethics Committee of Düzce University Faculty of Medicine (Decision Number: 2012/309).

Evaluation of Blood Samples: On the morning following the polysomnography, 3 mL of blood was collected for a complete blood count (CBC). The blood samples were collected in K3 EDTA tubes and measured within 2 hours using Pentra DX 120-Pentra XL 80 devices at the Microbiology-CBC Laboratory.

Sleep Study: Patients were questioned about symptoms of snoring and witnessed apnea. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale. Full-night polysomnography (SomnoMedics: Model: Somnoscreen PSG, Germany) was performed on all patients in the laboratory setting. The recorded parameters included three channels of electroencephalography (EEG), two channels of electrooculography (EOG), one channels of chin electromyography (EMG), oral and nasal airflow (thermistor and nasal cannula), thoracic and abdominal movements, body position, snoring, electrocardiography (ECG), and pulse oximetry (recorded for >6 hours). All recordings were manually scored in a computerized environment. Apnea was defined as a complete cessation of airflow in the mouth and nose for 10 seconds or longer, while hypopnea was defined as a decrease of airflow by more than 30% for 10 seconds or longer, accompanied by a 3% desaturation or aurasol. Patients with an apnea-hypopnea index (AHI) ≥ 5 were considered to have OSA

Evaluation of Patients: Based on the full-night polysomnography (PSG) data, patients were classified into groups according to the apnea-hypopnea index (AHI) as follows: no OSA (AHI < 5), mild OSA (AHI 5-15), moderate OSA (AHI 16-30), and severe OSA (AHI > 30). The groups were compared in terms of demographic and clinical characteristics, polysomnographic data, hemogram parameters, and MPV. Additionally, the changes in MPV were investigated in severe OSA patients who received regular CPAP treatment for one month and underwent hemogram follow-up (20 cases) to demonstrate the effect of OSA treatment on MPV.

Statistical Analysis: Demographic, clinical, and hemogram characteristics of patients were compared with the polysomnographic results using SPSS 21 software package. The chi-square test was used for the comparison of categorical data among the groups determined by polysomnography, while the Kruskal-Wallis test was used for the comparison of numerical data. Pairwise comparisons were performed using the Mann-Whitney U test with Bonferroni correction. Correlation analyses were conducted using Spearman's test. Comparisons before and after CPAP treatment in severe OSA patients were performed using the Wilcoxon test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 158 patients, including 51 females (32.3%) and 107 males (67.7%), were included in the study. The mean age of the patients was 51±13 (min-18, max-82) years. OSA was detected in 74.1% (117/158) of the patients (Figure 1). The comparison of some clinical characteristics according to the presence and severity of OSA is summarized in Table 1 and 2. Aspirin use was higher in moderate and severe OSA cases. The percentage of OSA symptoms such as snoring, habitual snoring, and witnessed apnea increased significantly with the severity of OSA.

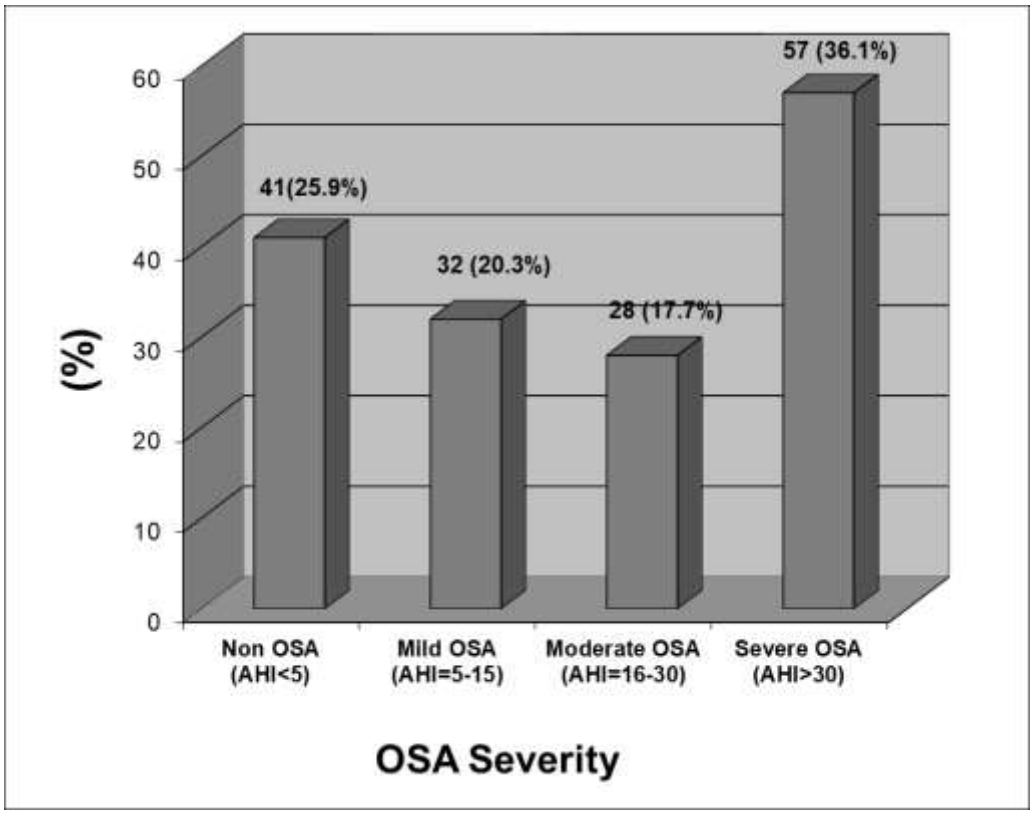

Figure 1. Polysomnographic results of the cases included in the study

Table 1. The comparison of some clinical characteristics (gender, smoking, alcohol use, diabetes mellitus, hypercholesterolemia, drugs used and OSA symptoms) according to the presence and severity of OSA

	N	Non OSA AHİ < 5	mild OSA AHİ=5-15	moderate OSA AHİ=16-30	Severe OSAS AHİ > 30	*p*
Gender *(Male/Female)*	158	22/19	24/8	20/8	41/16	*0.163*
Smoking						
Yes / quit / no	135	14/1/24	13/7/11	13/1/13	20/2/16	-
Alcohol use *n (%)*	134	4 (10.5%)	5(16.1%)	3(11.1%)	4(10.5%)	*0.878*
Diabetes Mellitus *n (%)*	133	6 (15.4%)	8(25.0%)	3(11.5%)	4(11.1%)	*0.393*
Hypercholesterolemia *n (%)*	130	6 (15.4%)	5(16.7%)	10(38.5%)	11(31.4%)	*0.095*
Drugs Used						
ACE inhibitor *n (%)*	120	3 (8.3%)	3 (10.7%)	6 (24.0%)	7 (22.6%)	*0.223*
Beta blocker *n (%)*	119	2 (5.7%)	1 (3.6%)	1 (4.0%)	4 (12.9%)	*0.443*
Ca channel blocker *n (%)*	119	1 (2.8%)	- (-)	1 (4.2%)	3 (9.7%)	*0.293*
Diuretic *n (%)*	120	1 (2.8%)	3 (10.7%)	6 (24.0%)	5 (16.1%)	*0.086*
Antiaggregant *n (%)*	120	1 (2.8%)	1 (3.6%)	6 (24.0%)	6 (19.4%)	-*
OSA Symptoms						
Habitual snoring *n (%)*	135	29 (72.5%)	23 (74.2%)	24 (92.3%)	36 (94.7%)	***0.018***
Witnessed apnea *n (%)*	132	20 (52.6%)	23 (76.7%)	20 (76.9%)	31(81.6%)	***0.026***

Ca: calcium; ACE: angiotensin converting enzyme; *p value was not shown due to expected value issue in Chi square test.

Table 2. Comparison of age, BMI, hemogram and some polysomnographic findings according to OSA severity

	Median (min-max)				*p*
	Non OSA (AHI < 5) N=41	**mild OSA (AHI=5-15) N=32**	**moderate OSA (AHI=16-30) N=28**	**Severe OSA (AHI > 30) N=57**	
Age *(years)*	47 (18-81)	53 (23-70)	53 (32-80)	52 (29-82)	*0.278*
BMI *(kg/m²)*	28.7 (19.7-47.5)	29.6 (22.2-62.2)	32.8 (25.0-50.3)	36.0 (25.4-71.2)	***<0.001***
Neck circumference *(cm)*	40 (24-48)	41 (37-45)	40 (37-46)	44 (36-51)	***0.005***
Epworth sleepiness scale	8 (0-22)	7 (0-22)	10 (1-24)	13 (1-24)	***0.014***
Polysomnographic findings					
Sleep efficiency *(%)*	87 (42-95)	88 (28-99)	90 (69-96)	89 (32-97)	*0.304*
Sleeping snoring *(%)*	22 (0 -70)	42 (0-87)	44 (2-88)	37 (2-81)	***0.007***
Sleep desaturation *(<%90 %)*	0 (0-84)	1 (0-14)	8 (3-67)	30 (0-99)	***<0.001***
Desaturation index *(hourly)*	1 (0-22)	7 (0-18)	20 (9-44)	55 (5-108)	***<0.001***
Complete blood count					
Hematocrit *(%)*	40.4 (28.6-46.3)	42.1 (27.6-53.6)	42.6 (36.8-51.9)	43.8 (32.1-54.4)	***0.001***
Hemoglobin *(g/dl)*	13.3 (9.1-16.8)	13.8 (8.2-17.9)	14.4 (12.5-17.0)	14.3 (9.9-17.1)	***0.024***
Platelets *(mm3'de bin)*	223 (102-344)	244 (150-423)	254 (99-354)	253 (117-524)	*0.283*
Mean platelet volume *(fL)*	10.30 (7.23-12.50)	10.50 (6.71-13.20)	10.10 (7.96-12.10)	9.30 (6.41-12.40)	***<0.001***

OSA; obstructive sleep apnea BMI; body mass index; AHI; apnea hypopnea index

The hemoglobin and hematocrit values from the hemogram parameters were found to increase parallel to the severity of OSA. There was no significant difference in platelet count according to the presence and severity of OSA. The mean platelet volume (MPV) was significantly lower in severe OSA cases compared to those without OSA and mild OSA cases (Figure 2).

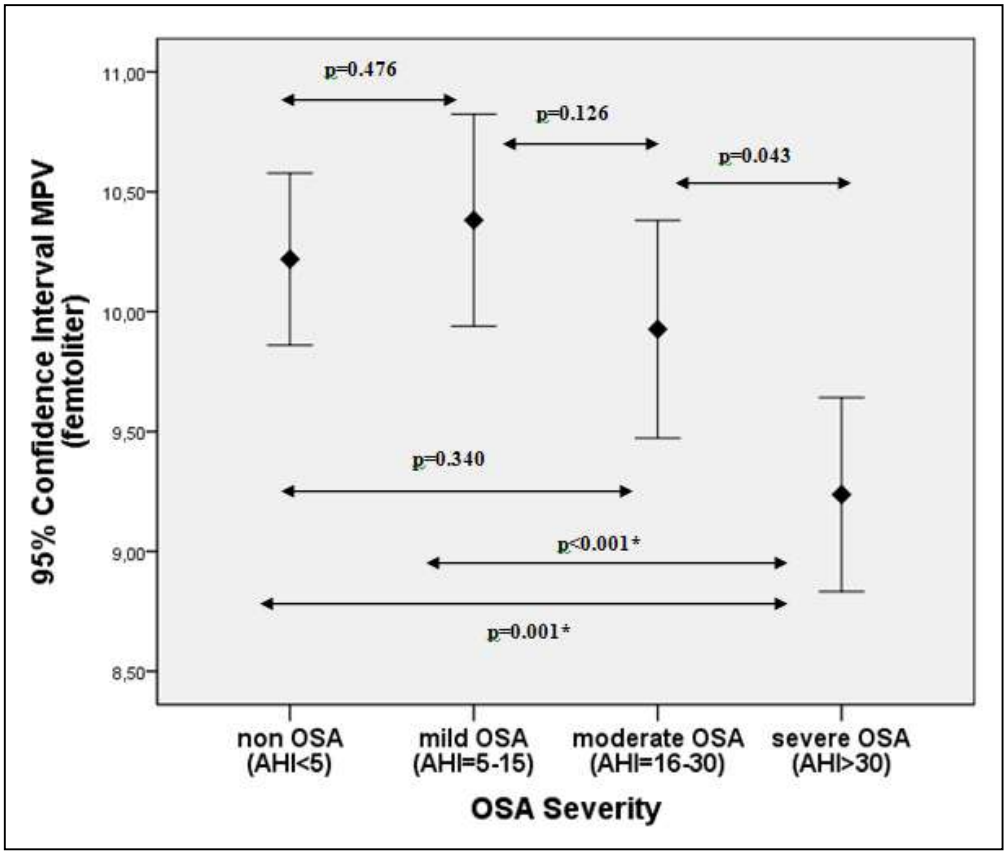

Figure 2. Comparison of mean platelet volume according to OSA severity. (Pairwise comparisons were made with Mann Whitney U test, and p significance value was determined as (0.05/6) < 0.0083 by applying Bonferroni correction)

When examining the correlation between patient characteristics and MPV, a negative correlation was observed between MPV and the apnea-hypopnea index (AHI), desaturation index, and the amount of oxygen saturation below 90% during sleep. On the other hand, a positive correlation was found between MPV and sleep efficiency and lactate dehydrogenase (LDH) levels.

As AHI increased, MPV significantly decreased (r=-0.241, p=0.003) (Figure 3). MPV significantly increased with increased sleep efficiency and LDH levels (r=0.207, p=0.015 and r=0.373, p=0.003, respectively). Additionally, MPV significantly decreased with an increase in the desaturation index and the amount of oxygen desaturation during sleep below 90% (r=-0.251, p=0.004 and r=-0.174, p=0.045, respectively).

Median MPV values were not statistically different according to gender, smoking, alcohol use, comorbidities and use of drug. However, the median MPV was found to be significantly lower in severe OSA cases. (Table 3 and Figure 2).

There were no significant differences between groups in terms of median red blood cell and platelet count, hematocrit percentage, and hemoglobin values before and after OSA treatment (Table 4). However, a significant decrease in MPV was observed after OSA treatment compared to before treatment (p=0.021, Figure 4).

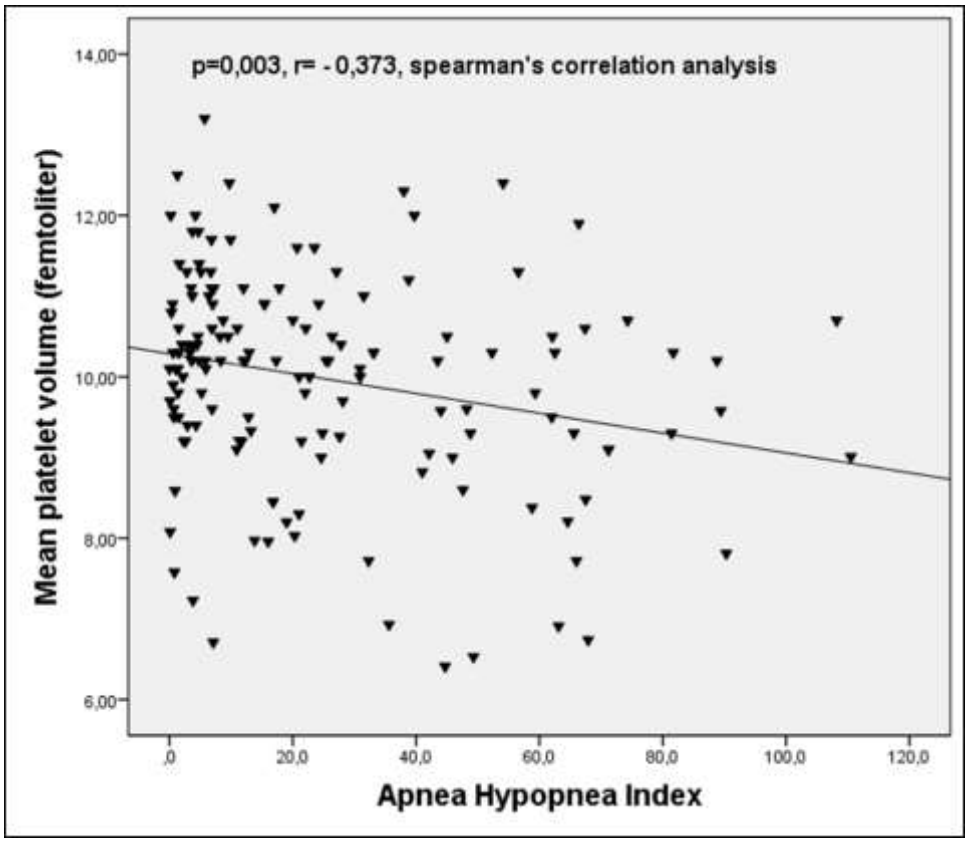

Figure 3. Correlation between MPV and apnea-hypopnea index

DISCUSSION

Contrary to the literature, study findings suggest that MPV decreases as AHI and desaturation index increase, and MPV is lower in cases with severe OSA (AHI>30) than in cases without OSA and with mild OSA (AHI<15). However, other results of this study are consistent with the literature and indicate that continuous positive airway pressure (CPAP) treatment applied to severe OSA patients significantly reduces MPV.

In many studies evaluating MPV from hemogram parameters according to the presence and severity of OSA, MPV was found to be significantly higher in patients with severe OSA compared to the control group (16-21). The common feature of these studies is that conditions such as diabetes and cardiovascular diseases, which have the potential to affect MPV, were used as exclusion criteria. On the other hand, some other studies concluded that MPV was not associated with the severity of OSA (22-24). In some of these studies, a healthy control group was used, while in others, as in our study, patients who underwent polysomnography test and had AHI<5 were included as the control group. Considering the differences in polysomnography indications, it can be said that the control group representing the non-OSA population in all these studies is quite heterogeneous.

Table 3. Comparison of MPV level according to some clinical features

	N	Mean Platelet Volume *(fL)* median (min-max)	*p*
Gender			
Male	107	10.10(6.41-13.20)	*0.224*
Female	51	10.20(7.58-12.50)	
Sigara			
No	64	10.25(6.41-12.50)	
Quit	11	10.10(6.71-13.20)	*0.631*
Yes	60	10.20(6.53-12.40)	
Alcohol use			
No	118	10.20(6.41-12.50)	*0.711*
Yes	16	10.15(8.48-13.20)	
Diabetes Mellitus			
No	112	10.20(6.41-12.50)	*0.287*
Yes	21	10.50(7.23-13.20)	
Hypercholesterolemia			
No	98	10.25(6.41-13.20)	*0.912*
Yes	32	10.20(7.72-12.50)	
ACE inhibitor			
No	101	10.20(6.41-13.20)	*0.487*
Yes	19	10.20(6.71-12.10)	
Ca channel blocker			
No	114	10.25(6.41-13.20)	*0.657*
Yes	5	10.20(7.71-10.70)	
Beta blocker			
No	111	10.30(6.41-13.20)	*0.147*
Yes	8	9.95(6.71-10.70)	
Diuretic			
No	105	10.30(6.41-13.20)	*0.243*
Yes	15	10.10(6.71-12.10)	
Antiaggregant			
No	106	10.25(6.41-13.20)	*0.134*
Yes	14	10.05(6.71-10.90)	
OSA severity			
Non (AHİ<5)	41	10.30(7.23-12.50)	
Mild (AHİ=5-15)	32	10.50(6.71-13.20)	***<0.001***
Moderate (AHİ=16-30)	28	10.10(7.96-12.10)	
Severe (AHİ>30)	57	9.30(6.41-12.40)	

Ca: calcium; ACE: angiotensin converting enzyme;

Table 4. Comparison of pre- and post-CPAP treatment hemogram parameters in severe OSA

	Median (min-max)		*p*
	Before Treatment N=20	**After Treatment N=20**	
Number of erythrocytes *(million per mm^3)*	5.15 (4.00-5.93)	4.94 (3.16-6.19)	*0.086*
Hematocrit *(%)*	44.1 (37.5-54.4)	43.6 (29.7-59.7)	*0.305*
Hemoglobin *(g/dl)*	14.4 (11.8-17.1)	14.3 (10.0-18.8)	*0.765*
Platelets *(thousand in mm^3)*	248 (176-317)	251 (169-386)	*0.513*
Mean Platelet Volume *(fL)*	8.31 (6.44-9.60)	7.92 (5.99-9.50)	***0.021***

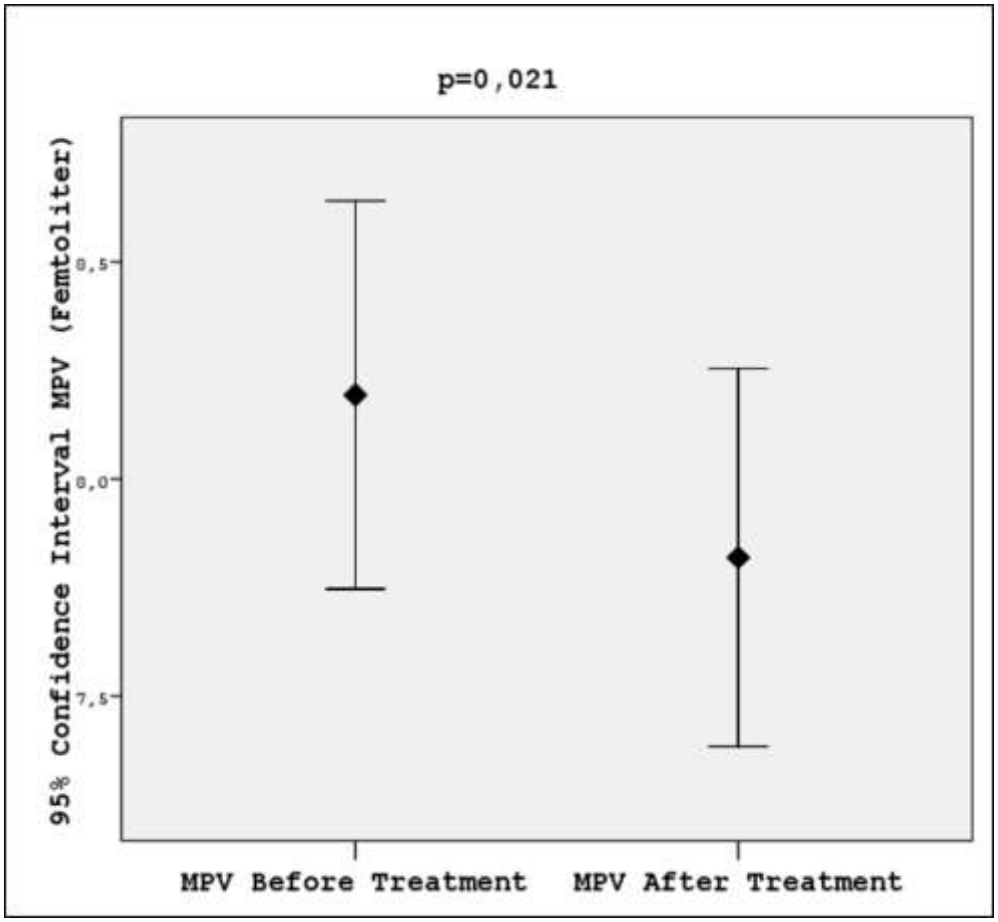

Figure 4. Comparison of MPV before and after treatment in severe OSA cases

In our study, we unexpectedly found significantly lower MPV values in the severe OSA group. The control group in our study did not consist of healthy volunteers, but rather of subjects with OSA symptoms, clinically thought to have OSA but with AHI < 5. In addition, some clinical conditions that have been shown to increase MPV in previous studies (diabetes, cardiovascular diseases, etc.) were not used as exclusion criteria in our study. Moreover, in studies related to this topic, patients taking antiaggregants were not included in the study because of the potential effect on MPV value, but in our study, all patients taking antiaggregants and other drugs were included without exception. In our study, the rates of antiaggregant use in the moderate and severe OSA groups (24% and 19.4%, respectively) were much higher than in the nonOSA and mild OSA groups (2.8% and 3.6%, respectively). Statistical evaluation could not be performed optimally because the number of subjects using antiaggregants was insufficient in the NonOSA and mild OSA groups (p value was not shown due to expected value issue in Chi square test - table 2). In addition, even though it did not reach statistical significance, median MPV values were lower in antiaggregant users compared to non-users in our study (10.05 fL vs. 10.25 fL, p=0.134, table 3). All these factors may explain the possible reasons why we paradoxically found lower MPV levels in the moderate and severe OSA group in our study.

Another reason for the conflicting results in the literature may be the differences in the methods and techniques used for MPV measurements. Platelet volume parameters are objective parameters in evaluating platelet size and can be examined during automated complete blood count without additional cost (15). Platelet shape and ultrastructure vary depending on the anticoagulant used, ambient temperature, and the method employed (25). Normal MPV values are measured as 4.5-8.5 fL (femtoliters) when sodium citrate is used as an anticoagulant, whereas when Ethylenediaminetetraacetic acid (EDTA) is used, this value is measured as 7-13 fL (26). Platelets collected with EDTA are spherical in shape, while those collected with citrate are discoid. EDTA causes platelets to swell over time. MPV can be measured using impedance or optical methods. When impedance measurement is performed using EDTA, MPV increases over 24 hours, with a maximum value reached after 2 hours. When an optical system is used, MPV decreases by 10% within 2 hours when EDTA is used (27). When citrate is used as an anticoagulant, MPV remains stable over time. At 37°C, OTH changes by 3% in 3 hours, while at room temperature, MPV increases by 20% (22). Dastjerdi et al., measurements using

EDTA and sodium citrate and showed no significant difference (28). Bath et al., considering that MPV measurements were previously performed using EDTA, which causes platelet swelling, measured MPV using sodium citrate. In this study, no difference was found between hypertensive patients and healthy control group (29). In our study, MPV were measured using the impedance measurement method in the Microbiology-CBC Laboratory within 2 hours after collecting 3 ml of blood in a K3 EDTA tube in the morning following polysomnography. In the studies conducted by Karakaş and Varol, the method used for MPV measurement, anticoagulant (EDTA), and the duration of blood collection were the same as the method, anticoagulant, and duration we used in our study (16, 18).

When impedance measurement is performed using EDTA, MPV increases over time. The lack of attention to the time interval between blood collection and MPV measurement in MPV-related studies may be another important reason for confusing results.

It would be more valuable to evaluate the same cases with the same method before and after treatment (self-control) rather than comparing with an insufficiently matched control group to reveal a causal relationship between MPV and OSA.

Varol et al. found that MPV values were significantly higher in severe OSA patients compared to the control group. They also showed that 6 months of CPAP treatment led to a significant decrease in MPV values in severe OSA patients (30). In our study, although MPV values did not show a positive correlation with OSA severity, it was shown that 1-month CPAP treatment significantly reduced MPV in severe OSA patients. In our study, platelet counts in OSA patients before and after CPAP treatment were statistically similar. Considering that the platelet life is 10 days, 1 month of CPAP treatment was considered sufficient. The results support the idea that CPAP therapy improves possible increased platelet activation in OSA.

In studies conducted on pediatric patient groups, high MPV levels were found in OSA patients, and decreases in MPV values were demonstrated after treatments such as adenotonsillectomy (31, 32). In recent studies, Ulusoy and colleagues found that MPV values were significantly higher in OSA patients. However, in this study, contrary to our study, a 1-month PAP treatment was insufficient to decrease elevated MPV values (20). In a study investigating the changes in MPV values in OSA patients who underwent uvulopalatal flap (UPF) surgery, a significant decrease in platelet volume was observed in OSA patients after UPF surgery (33). In another study by Özdemir and colleagues (34), contrary to all other studies, a 3-month CPAP treatment in OSA patients resulted in a statistically significant increase in MPV (before treatment 9.25±1.55, after 3-month CPAP treatment 9.66 ±1.22, p=0.010).

In another study by Kutlucan et al., which included a large population of 2298 individuals, the correlation between metabolic syndrome and its components with MPV was investigated in obese individuals. The presence of metabolic syndrome and its components did not make a significant difference in MPV values in obese patients with a BMI ≥ 30 kg/m2 (35). In our study, there was no statistically significant difference between MPV and BMI, but a statistically significant higher BMI was found in the severe OSA group.

In a retrospective study conducted by Binita et al., the relationship between platelet activity measured by MPV, metabolic syndrome, and diabetes was examined. A total of 13,021 patients between 1999 and 2004 were included in the study. In this study, MPV was found to be statistically significantly higher in diabetic patients compared to non-diabetic individuals and in abdominal obesity, indicating a strong and independent association between MPV and the presence and severity of diabetes (36). In our study, the presence of diabetes did not affect MPV in OSAS patients.

Although there is no study specifically related to LDH and OTH in the literature, it has been reported that LDH increases in diseases associated with thrombocytosis (37, 38). In our study, platelet counts were similar between the pre- and post-treatment groups, and it was observed that MPV statistically significantly increased as LDH levels increased (r=0.373; p=0.003). Further studies are needed to investigate the correlation between LDH and MPV in OSAS patients.

The most powerful aspect of our study compared to other studies is that the control group included all consecutive patients who underwent full PSG, whose clinical and demographic characteristics were similar to those of OSA patients but who were proven not to have OSA by PSG. Another important advantage of the study is the good methodological standardization in MPV measurements. The most significant limitation of this study is the relatively small number of cases in the follow-up after CPAP treatment.

CONCLUSION

The results of the study do not support an increase in MPV and hence platelet activation in severe OSA patients compared with those without OSA. However, the results suggest that one month of CPAP treatment reduces MPV and thus platelet activation in severe OSA patients. Further controlled, prospective studies including treatment outcomes are needed on this subject.

Compliance with Ethical Standards

Funding: This study received no funding.

Conflict of Interest: The authors declared no potential conflict of interest with respect to the

research, authorship, and/or publication of this article

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Duzce University Medical Faculty Non-Invasive Clinical Trials Ethics Committee (Decision Number: 2012/309).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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RESEARCH ARTICLE

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Urodynamic Findings of the Patients with Parkinson's Disease: A Single Tertiary Center Results

ABSTRACT

Objective: In Parkinson's disease (PD), lower urinary tract symptoms (LUTS) are common with a prevalence ranging from 25% to 57%. Patients who are resistant to medical treatment for LUTS may require urodynamic examination and pressure flow study (UD-PFS) to better comprehend the bladder's dynamics. To be able to understand the pathophysiology of LUTS, UD-PFS examinations should be performed. In this study, the demographics and clinical properties of PD patients were presented along with their UD-PFS examinations.

Materials and Methods: The data of 155 patients with PD followed up between 2010-2020 were retrospectively analyzed. UD-PFS was applied to 42 PD patients resistant to medical treatment of LUTS. Patients' demographic and clinical data with their UD-PFS findings were investigated separately.

Results: Twenty-eight of the patients underwent UD-PFS were male, and 14 were female. In UD, the first urinary sensation was 86.00±68.77cc, and the maximum cystometric capacity was 322.07±194.25cc. Sixteen patients had a hypo-compliant bladder, 25 (59.5%) had a normo-compliant bladder. In PFS, Q max and peak detrusor pressure during voiding were 12.72±10.08 mL/sec and 43.93±15.56 cm-H2O, respectively. Stress-type urinary incontinence was detected in 6 (15%) of the patients. When evaluating the detrusor activity, neurogenic detrusor overactivity was observed in 18 (44%) patients, detrusor areflexia in 8 (19%) and normal UD-PFS in 16 (22%) patients.

Conclusions: The majority of the PD patients presented with neurogenic detrusor overactivity accompanied by diminished bladder capacity and hypersensitivity. In the selected PD patients who are resistant to medical treatment with LUTS clinics, UD-PFS provides useful scientific information about the LUTS clinics of patients and may be helpful in treatment management.

Keywords: Urodynamic Examination, Pressure Flow Study, Parkinson's Disease.

Parkinson Hastalarında Ürodinamik İnceleme Bulguları: Tek Tersiyer Merkez Sonuçları

ÖZET

Amaç: Parkinson hastalığında (PH), alt üriner sistem semptomları (AÜSS) yaygın olarak, %25 ila %57 arasında değişen bir prevalansla görülür. AÜSS için medikal tedaviye yanıt vermeyen hastalarda mesane dinamiklerini daha iyi anlamak için ürodinamik inceleme ve basınç akış çalışması (ÜD-BAÇ) gerekebilir. ÜD-BAÇ incelemeleri AÜSS patofizyolojisinin anlaşılmasına katkı sağlayabilir. Bu çalışmada Parkinson hastalarının demografik ve klinik bulgularının ÜD-BAÇ tetkiklerinin sonuçları ile birlikte değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2010-2020 yılları arasında takip edilen 155 Parkinson hastasının verileri retrospektif olarak incelendi. AÜSS'ları medikal tedaviden fayda görmeyen 42 Parkinson hastasına ÜD-BAÇ uygulandı. Hastaların klinik ve demografik verileri ile ÜD-BAÇ bulguları ayrı ayrı değerlendirildi.

Bulgular: ÜD-BAÇ uygulanan hastaların 28'i erkek, 14'ü kadındı. ÜD'de ilk idrar hissi 86.00±68.77cc, maksimum sistometrik kapasite 322.07±194.25cc idi. 16 hastada hipo-kompliyan mesane, 25'inde (%59,5) normo-kompliyan bir mesane vardı. BAÇ'ta işeme fazındaki Qmax ve maksimum detrüsör basıncı sırasıyla 12,72±10,08 mL/sn ve 43,93±15,56 cm-H2O idi. 6 (%15) hastada stres tip üriner inkontinans saptandı. Detrusor foksiyonu değerlendirildiğinde ise 18 (%44,0) hastada nörojenik detrusor aşırı aktivitesi, 8 (%19) hastada detrusor arefleksi ve 16 (%22) hastada normal ÜD-BAÇ saptandı.

Sonuç: PD hastalarının çoğunda azalmış mesane kapasitesi ve hipersensitivite ile nörojenik detrüsör aşırı aktivitesi vardı. AÜSS klinikleri ile medikal tedaviye dirençli PH grubundaki seçilmiş hastalarda ÜD-BAÇ, hastaların AÜSS klinikleri hakkında değerli bilimsel veriler sağlar ve tedavi yönetiminde faydalı olabilir.

Anahtar Kelimeler: Ürodinamik İnceleme, Basınç Akım Çalışması, Parkinson Hastalığı.

INTRODUCTION

Parkinson disease (PD) is a neurodegenerative condition characterized by the aberrant accumulation of alpha-synuclein protein in the central and peripheral nervous systems (1). Parkinson's disease is one of the most prevalent neurodegenerative conditions, affecting 100 to 180 people per 100,000 (2). Motor symptoms (tremors, rigidity, and bradykinesia) are frequently predominate, while commonly observed non-motor symptoms include neuro-psychiatric disorders, lower urinary tract symptoms (LUTS) and sleep disorders (3). The reported incidence of voiding dysfunction in Parkinson's disease patients ranges between 37 and 70% (4).

In PD patients, LUTS can be variable and of varying degrees. The presence of LUTS in PD is linked to decreased quality of life, falls, and hospitalization (5). Overactive bladder (OAB) symptoms, which are urine urgency, frequency, and nocturia, with or without incontinence, are the most common LUTS in PD patients (6). According to studies, 57–83% of patients exhibit storage symptoms, but only 17–27% of patients exhibit voiding symptoms (7). Patients who do not respond to medical treatment for LUTS may require a urodynamic examination and pressure flow study (UD-PFS) to better comprehend the bladder's dynamics. UD-PFS examinations may aid in the comprehension of the pathogenesis of LUTS in PD patients.

In this study, we aimed to evaluate the demographic and clinical characteristics of PD patients along with their UD-PFS examinations.

MATERIAL AND METHODS

With the approval of a local ethical committee (Protocol Number: 2021.17.01.17), the data of 155 patients diagnosed with PD who were followed up in Urology Clinic of Tekirdağ Namık Kemal University between 2010 and 2020 were retrospectively analyzed. Patients who were excluded from the study included those who were incompatible with the diagnosis of PD or had external diseases that could explain the symptoms. UD-PFS was applied to 42 PD patients who did not benefit from the medical treatment of LUTS. International Continence Society (ICS) standards were applied in all urodynamic studies (8). Before the examination, patients were instructed to void their bladders, and the initial procedure was to quantify the postvoid residual (PVR) volume using a urethral catheter. Filling cystometry was then conducted at a rate of 10 mL/min with saline solution or at lower rates in cases of severe detrusor overactivity (DO) or known small functional capacity. Thereafter, a PFS was conducted after the urodynamic evaluation. The PVR was reevaluated following the pressure-flow research with a urethral catheter again. A specialist in urodynamics conducted the evaluation of all the urodynamic traces. Demographic (age, gender, follow-up period) and clinical data (incontinence, urgency) and following urodynamic findings according to ICS guidelines of the patients were investigated (8); first urinary sensation of the filling bladder (mL), maximum cystometric capacity (mL), maximum detrusor pressures at filling and voiding phases (cm H2O), post-voiding residual volumes (mL), and pressure flow study parameters (Qmax, mL/sec, and PdetQmax, cm H2O) were evaluated separately.

RESULTS

A total of 42 patients, 28 males and 14 females, underwent UD-PFS. The mean ages were 65.85 years, and the mean follow-ups were 69.34 months. Most of the patients had urgency (52.4%) and urge type-incontinence (66.7%). The patient demographic variables are given in Table 1.

Table 1. Patient demographics of the PD patients with UD examinations

Variable	Value
Age (mean ± SD)	65.85 ± 8.70
Gender (n, %)	
Male	28 (66.7%)
Female	14 (33.3%)
Follow up period (months) (mean ± SD)	69.34 ± 30.1
Body-Mass Index (BMI) (mean ± SD)	25.4 ± 4.6
Urgency (n, %)	
Yes	22 (52.4%)
No	20 (47.6%)
Urge-Incontinence (n, %)	
Yes	28 (66.7%)
No	14 (33.3%)
Stress-Incontinence (n, %)	
Yes	6 (14.3%)
No	36 (85.7%)

SD: standard deviation

The mean first urinary sensations of the patients were 86.0 mL. Among the patients with PD, most of them had normo-compliant bladders and only 1 patient had hypercompliant bladder. The mean maximum cystometric capacities were 322.07mL. Maximum detrusor pressures at the filling phase were 23.74 and at the voiding phase were 43.93 cm H_2O. The mean post voiding residual volumes were 92.29 mL and Qmax were 12.72 mL/sec. A total of 8 patients (19.0%) had obstruction during the urination phase. The UD-PFS findings of the patients can be seen in Table 2.

About 15% of the patients had stress-type urinary incontinence. Four of them were female (28.6%), and two (7.1%) of them were male. In patients with stress urinary incontinence, 2 of them had neurogenic detrusor overactivity, 3 of them had normal detrusor activity, and 1 of them had detrusor areflexia. In the total patient group, about 38.1% of

the patients had neurogenic detrusor overactivity, 19.0% had detrusor areflexia, and 42.9% of them had normal detrusor functioning.

Table 2. Urodynamic findings of the PD patients

Variable	Value
First urinary sensation (mL) (mean ± SD)	86.00 ± 68.77
Maximum Cystometric Capacity (mL) (mean ± SD)	322.07 ± 194.25
Maximum Detrusor Pressure at filling (cm H_2O) (mean ± SD)	23.74 ± 20.55
Maximum Detrusor Pressure at voiding (cm H_2O) (mean ± SD)	43.93 ± 15.56
Compliance (n, %)	
Hypo-compliant	16 (38.0%)
Normo-compliant	25 (59.5%)
Hyper-compliant	1 (2.5%)
Post-voiding Residual Volumes (mL) (mean ± SD)	92.29 ± 98.82
Qmax (mL/sec) (mean ± SD)	12.72 ± 10.08
Detrusor pressure at maximum flow (cm H_2O) (mean ± SD)	43.93 ± 15.56

SD: standard deviation

DISCUSSION

Parkinson's disease patients exhibited multiple forms of bladder dysfunction, as determined by urodynamic testing. The disease severity and duration increase the prevalence of pathological urodynamic findings (9). Nevertheless, only postvoid residual urine volume was correlated with disease severity. Thus, lower urinary tract symptoms may be more sensitive for detecting minor differences in bladder dysfunction than urodynamic parameters, despite the fact that urodynamic evaluation is essential for distinguishing voiding disorder etiologies (10). As indicated in all neurological diseases, in PD treatment, treatment protocols can be arranged by providing information about bladder functions with a urodynamic examination accompanied by PFS.

The overactive bladder is the most prevalent urinary symptom in Parkinson's patients with LUTS. (11). Our study population's results are also in correlation with that. Ransmayr et al. found that neurogenic detrusor overactivity (NDO) was present in 46% of patients with PD, which is very similar to our study population's results (12). About 27–63.9% of patients with PD have lower urinary tract dysfunction, which is substantially higher than in healthy controls (13). In early publications, this ratio was detected as 38-71% (14). Before initiating treatment, individuals with PD and complicated LUTS should undergo a comprehensive urodynamic evaluation, including cystometry, sphincter EMG, uroflowmetry, electromyelography, and ultrasonography (15). To what extent PD contributes to LUTS, however, has been difficult to determine. Because of benign prostatic hyperplasia (BPH), not only PD patients but also men over the age of 60 may experience urinary obstruction symptoms as a result of their condition. Stress urinary incontinence can occur in females of elderly age (13). It is difficult to distinguish whether these conditions are due to Parkinson's or the result of a natural aging process.

Urgency is another common complaint among patients with PD. In the literature, it occurs in 33-54% of the patients (16). It is believed that overactive bladder (detrusor) is the primary cause of urinary urgency, frequency, and incontinence. Pressure-flow analysis of the voiding phase in PD has revealed reduced detrusor activity and low Qmax values. (40% of men vs. 66% of women) (17). There is a relationship between a weak detrusor and the disease's stage. But again, BPH might be a co-existing factor that also causes voiding difficulty. Also, obstruction itself can cause detrusor overactivity and urgency.

We were only able to evaluate the urodynamic findings of PD patients referred to the urology clinic for LUTS or routine urological examination in this study. Therefore, the sample population could not include all PD patients. Due to the invasive character of urodynamic studies, it is unethical to conduct them on all PD patients. When patients with these conditions are evaluated, the relationship between bladder compliance and PD is a subject that has not been studied much in the literature. Otherwise, there are some studies with some links that lightened to other neurological disorders (18). In our study, while normo-compliant bladder was detected in more than half of the patients, hypo-compliant bladder was also found in a substantial number of cases. Studies with larger numbers of patients are needed to determine whether this cause-and-effect relationship is due to the disease itself or the natural process of aging.

The prevalence of stress urinary incontinence ranges from 4% to 35% in women (19). The rate of stress urinary incontinence in women in our patient population was similar to that in the general population. Rates of stress urinary incontinence appear to be similar in the general population of women with PD (20). In males, this ratio is found to be less than 10% (21) which is again in correlation with our study's findings.

Our research has some limitations. It is retrospective and has a nonrandomized design. Our findings may have been influenced by the fact that this was a single-center study from a tertiary referral center. We were unable to conduct multivariate analysis to examine success and complication predictability with greater precision due to the relatively small sample size and inherent lack of statistical power. Even urology clinics with a high patient volume were able to publish their results with a small sample size, according to the literature. We believe that future multi-centric studies documenting national data similar to our study will allow enriching the national library. In

light of this, we believe that the number of study participants adds significant scientific data to the national data library. The absence of validated questionnaires related to PD to assess LUTS is another significant limitation. We think that such studies will serve as a pioneer for the creation of questionnaires. Lastly, the lack of evaluation of how urodynamic findings may influence treatment decisions and outcomes may be regarded as a significant limitation. The prospective randomized studies are necessary to understand the treatment outcomes.

CONCLUSION

As a result of UD-PFS results of individuals with PD, it was found that the majority of patients had neurogenic detrusor hyperactivity with hypersensitivity and decreased bladder capacity. In the selected group of PD patients who are resistant to medical treatment in accordance with their LUTS clinics, to be able to provide valuable scientific information about the patients' LUTS clinics and to have beneficial treatment management, a UD-PFS should be performed.

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RESEARCH ARTICLE

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Comparison of CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ Score Estimation of In-Hospital Mortality Among COVID-19 Patients

ABSTRACT

Objective: This study aims to compare of CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ score estimation of in-hospital mortality among COVID-19 patients and find a new scoring system that can better predict the hospital mortality by adding some laboratory parameters to the CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ scores.

Materials and Methods: This is a cross-sectional study. A total of 1076 COVID-19 patients with confirmed COVID-19 PCR tests were included from September 2020 to March 2021. Age, sex, comorbidity, laboratory, survival times, and death status of the patients were recorded. The scores CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ of each patient were calculated. A new mortality prediction score was created to establish the most effective model with logistic regression analysis, including laboratory values.

Results: Of the 1076 patients hospitalized for COVID-19, 15.1% died, while 84.9% survived. There was no significant difference between the two groups in sex. All comorbidities were significantly higher in the deceased than in the survivors ($p<0.001$). The survivors' hemoglobin, thrombocyte, and eGFR values were significantly higher. The C-reactive protein (CRP), aspartate aminotransferase (AST), and neutrophil-to-lymphocyte ratio (NLR) were found to be associated with mortality, and the CAN-$R_2CHA_2DS_2VASc$ score was created by including these three laboratory parameters. The ROC curves of the scores CHA_2DS_2VASc (AUC=0.810), $R_2CHA_2DS_2VASc$ (AUC=0.824), and CAN-$R_2CHA_2DS_2VASc$ (AUC=0.909) were analyzed. The CAN-$R_2CHA_2DS_2VASc$ score was superior to other scores ($p<0.001$). The sensitivity and specificity of the CAN-$R_2CHA_2DS_2VASc$ score were 79.8% and 86.5%, respectively, while the criterion was >6 points.

Conclusions: The CAN-$R_2CHA_2DS_2VASc$ score is a useful tool for estimating hospital mortality in COVID-19 patients. The CAN-$R_2CHA_2DS_2VASc$ score was superior to the $R_2CHA_2DS_2VASc$ and CHA_2DS_2VASc score in predicting in-hospital mortality.

Keywords: Mortality, Hospitalization, COVID 19, Survival, Risk Factors, Comorbidity.

COVID-19 Hastalarında Hastane İçi Mortalitenin CHA_2DS_2VASc ve $R_2CHA_2DS_2VASc$ Skor Tahmininin Karşılaştırılması

ÖZET

Amaç: Bu çalışma, COVID-19 hastalarında hastane içi mortalitenin CHA_2DS_2VASc ve $R_2CHA_2DS_2VASc$ skor tahminini karşılaştırmayı ve CHA_2DS_2VASc ve $R_2CHA_2DS_2VASc$ skorlarına bazı laboratuvar parametreleri ekleyerek hastane mortalitesini daha iyi tahmin edebilen yeni bir skorlama sistemi bulmayı amaçlamaktadır.

Gereç ve Yöntem: Bu bir kesitsel çalışmadır. Eylül 2020'den Mart 2021'e kadar COVID-19 PCR testleri doğrulanmış toplam 1076 COVID-19 hastası dahil edildi. Hastaların yaş, cinsiyet, komorbidite, laboratuvar, hayatta kalma süreleri ve ölüm durumları kaydedildi. Her hastanın CHA_2DS_2VASc ve $R_2CHA_2DS_2VASc$ skorları hesaplandı. Laboratuvar değerleri de dahil olmak üzere lojistik regresyon analizi ile en etkili modeli oluşturmak için yeni bir ölüm tahmin skoru oluşturuldu.

Bulgular: COVID-19 nedeniyle hastaneye yatırılan 1076 hastanın %15,1'i öldü, %84,9'u hayatta kaldı. İki grup arasında cinsiyet açısından anlamlı fark yoktu. Ölenlerde tüm komorbiditeler yaşayanlara göre anlamlı derecede yüksekti ($p<0.001$). Hayatta kalanların hemoglobin, trombosit ve eGFR değerleri anlamlı olarak daha yüksekti. C-reaktif protein (CRP), aspartat aminotransferaz (AST) ve nötrofil-lenfosit oranı (NLR) mortalite ile ilişkili bulundu ve bu üç laboratuvar parametresi dahil edilerek CAN-$R_2CHA_2DS_2VASc$ skoru oluşturuldu. CHA_2DS_2VASc (AUC=0,810), $R_2CHA_2DS_2VASc$ (AUC=0,824) ve CAN-$R_2CHA_2DS_2VASc$ (AUC=0,909) skorlarının ROC eğrileri analiz edildi. CAN-$R_2CHA_2DS_2VASc$ skoru diğer skorlardan üstündü ($p<0.001$). CAN-$R_2CHA_2DS_2VASc$ skorunun duyarlılığı ve özgüllüğü sırasıyla %79,8 ve %86,5 iken, kriter >6 puandı.

Sonuç: CAN-$R_2CHA_2DS_2VASc$ skoru, COVID-19 hastalarında hastane mortalitesini tahmin etmek için yararlı bir araçtır. CAN-$R_2CHA_2DS_2VASc$ skoru, hastane içi mortaliteyi tahmin etmede $R_2CHA_2DS_2VASc$ ve CHA_2DS_2VASc skorundan üstündü.

Anahtar Kelimeler: Ölüm Oranı, Yataklı Tedavi, COVID-19, Sağ Kalım, Risk Faktörleri, Eşzamanlı Hastalık.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was defined as a pandemic by the World Health Organization on 11 March 2020, after its first detection in December 2019 in Wuhan, China, as the causal agent of COVID-19 disease (1, 2). COVID-19 remains a serious health problem worldwide. Although it mainly causes pneumonia in the lung, it can cause illness in more than one organ system (3). Age, male sex, and common cardiovascular comorbidities are associated with worse outcomes, and thromboembolic complications play an important role in the clinical course of these patients (4-6).

SARS-CoV-2 is a single-stranded RNA virus that enters cells by binding to angiotensin-converting enzyme two receptors found mainly in the lungs, heart, and vessels of the human body (7). Endothelial dysfunction is believed to play an essential role in the pathogenesis of thromboembolic events in COVID-19 (8, 9). The SARS-CoV-2 infection has been suggested to induce a process known as immunothrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade, leading to the formation of intravascular clots in small and larger vessels (10, 11).

The $R_2CHA_2DS_2VASc$ scores, created by combining the CHA_2DS_2VASc score and the estimated glomerular filtration rate (eGFR), are simple scoring systems that are commonly used to predict the risk of systemic thromboembolism in patients with atrial fibrillation (AF) (12, 13). These risk scores have been shown to predict morbidity and mortality in various clinical conditions other than AF (14, 15). Taking into account the worse prognosis of the male sex in COVID-19 patients, it has been shown that the modified CHA_2DS_2VASc score, obtained by assigning 1 point to the male gender instead of the female gender, predicts in-hospital mortality (16-18). Renal dysfunction is also associated with increased morbidity and mortality in COVID-19 patients (19, 20). The R2CHA2DS2-VASc score, created by including renal (R) functions in the CHA2DS2VASc score, also predicts mortality in COVID-19 patients (16, 21). Similar to these, many other scoring systems have been created, including clinical, laboratory, and physiological parameters (20, 22-24). COVID-19 is a systemic infectious disease that causes cell destruction and inflammation. A new scoring system in which laboratory values that indicate cell damage and inflammation are included will be more effective in determining the prognosis. The aim is to compare CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ score estimation of in-hospital mortality among COVID-19 patients and find a new scoring system that can better predict hospital mortality by adding some laboratory parameters to the CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ scores.

MATERIAL AND METHODS

This retrospective study was conducted at Health Sciences University Samsun Training and Research Hospital and included 1200 consecutive patients whose COVID-19 nasopharyngeal swab samples were positive by real-time reverse transcriptase-polymerase chain reaction (PCR) between September 1, 2020 and March 31, 2021. Those with active cancer, those receiving chemotherapy-radiotherapy treatment, immunosuppressive therapy for various reasons, those with severe liver disease, coagulation disorders, rheumatological diseases (Systemic Lupus Erythematosus, Behçet's Syndrome, Rheumatoid Arthritis, etc.), those using oral contraceptives and those aged under 18 years were excluded from the study. A total of 1076 patients with COVID-19 who met the appropriate criteria were included in the study. This study was carried out according to the Declaration of Helsinki, registered with the Ministry of Health Scientific Research COVID-19 Committee, and approved by the Local Ethics Committee.

Demographic, laboratory, and clinical information was obtained from patient electronic data at the emergency department and COVID-19 clinics, accessible at the individual patient level. Demographic and clinical data included age, sex, presence of prior diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, cardiovascular disease, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, chronic kidney disease, and smoking status. Detailed biochemical data and complete blood counts of all patients were obtained from the emergency department and the COVID-19 clinics. The estimated glomerular filtration rate (eGFR) was calculated using the Modified Diet in Renal Disease equation in kidney disease, using the mean of two different serum creatinine measurements in patients with steady-state renal function (one on emergency room admission and the second on the first day of pandemic hospital admission). Patients with acute kidney damage were excluded and an eGFR value <60 ml/min/1.73 m^2 was accepted as renal failure.

The CHA_2DS_2VASc and $R_2CHA_2DS_2VAScs$ scores of each patient were calculated during their hospitalization using clinical data from electronic medical health record history and routine biochemical tests. CHA_2DS_2VASc was calculated by giving 1 point for congestive heart failure, hypertension, age 65-74 years, diabetes mellitus, vascular disease, male sex, and 2 points for ischemic stroke history and/or transient ischemic attack (TIA) and age ≥75 years. When calculating the M-$R_2CHA_2DS_2VAScs$ score, the eGFR values >60 ml/min/1.73m^2, between 30-60 ml/min/1.73 m^2 and <30 ml/min/1.73m^2 were determined to be 0, 1 and 2 points, respectively. In addition to the CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ scores, binary logistic regression analysis was used to select laboratory variables affecting the risk of in-hospital mortality. Parameter estimates were obtained using the stepwise selection method to identify the most effective model and variables that included all possible variations.

C-reactive protein (CRP) levels were evaluated according to the classification of 3-10 mg/L normal or minor elevation, 10-100 mg/L moderate elevation, and >100 mg/L marked elevation (25). These levels were evaluated as 0, 1, 2 points, respectively. Aspartate aminotransferase (AST) levels were evaluated as < 40 U/L normal, 40-80 U/L mild elevation, and >80 U/L moderate or marked elevation (26). These levels were evaluated as 0, 1, and 2 points, respectively. Since there is no standardized classification for AST value, an increase of 2 times the upper limit of normal was evaluated as moderate or marked. The Neutrophil/Lymphocyte ratio (NLR) was evaluated according to the classification of <6 normal, 6-9 mild stress, >9 critically ill patients (27). These levels were evaluated as 0, 1, and 2 points, respectively.

Statistical Analysis: Statistical analysis was performed using The conformity of continuous variables to the normal distribution was examined using visual graphics and the Kolmogorov–Smirnov/Shapiro–Wilk test. Continuous variables were presented as median

(quartile 1- quartile 3) and categorical variables as frequency and percentage. When appropriate, categorical variables were analyzed using the chi-square or Fisher's exact test. Continuous variables were analyzed using the Mann-Whitney U test.

In addition to the CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ scores, binary logistic regression analysis was used to select laboratory variables affecting the risk of in-hospital mortality. Parameter estimates were obtained using the stepwise selection method to identify the most effective model and the variables that included all possible variations. Cox & Snell R^2, Nagelkerke R^2, accuracy, and p-values of the CAN-$R_2CHA_2DS_2VASc$ model created in this way were evaluated. The significance level was accepted as $p<0.05$. IBM SPSS Statistics version 26.0. was used for these analyses.

Receiver operating characteristic (ROC) analysis was performed for scores. The area under the curve (AUC) was evaluated. AUC and 95%CI values were given. The Delong test was used for the comparison of the ROC curve. The point of criterion at which sensitivity and specificity were optimal was selected using the Youden index. MedCalc® Statistical Software trial version 20.115 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022) was used for these analyses.

RESULTS

While 15.1% (n=163) of 1076 patients hospitalized for COVID-19 died, 84.9% (n=913) survived. There were no significant differences between the two groups in sex, and 46.3% of the survivors and 41.7% of the deceased were women (p=0.276). There was a significant difference between survivors and deceased in terms of age (p<0.001). While 43.6% of the deceased were ≥75 years old, 27.6% were in the 65-74 age range, and 28.8% were in the 18-64 age range. On the other hand, 66.0% of the survivors were in the 18-64 age range. Of those who died, 28.8% had congestive heart failure, 85.3% hypertension, 14.7% Stroke/TIA/thromboembolism, 33.1% vascular disease, 50.9% diabetes, 57.1% chronic renal failure, and 17.8% COPD comorbidity. All comorbidities were significantly higher in the deceased than in the survivors (p<0.001). Initial laboratory evaluation revealed that the survivors' hemoglobin, thrombocyte, and eGFR values were significantly higher. In contrast, all other laboratory parameters in Table 1 were significantly higher in the deceased.

Table 1. Characteristics and initial laboratory results of COVID-19 patients

Parameters	**Survivor n=913**	**Non-survivor n=163**	**p-values**
Sex (Female), n (%)	423(46.3)	68(41.7)	0.276
Age group, n (%)			
18-64 years	603(66.0)	47(28.8)	<0.001
65-74 years	201(22.0)	45(27.6)	
≥75 years	109(12.0)	71(43.6)	
Comorbidities, n (%)			
Congestive heart failure	48(5.3)	47(28.8)	<0.001
Hypertension	393(43.0)	139(85.3)	<0.001
Stroke/TIA/thromboembolism	15(1.6)	24(14.7)	<0.001
Vascular disease	109(11.9)	54(33.1)	<0.001
Diabetes	242(26.5)	83(50.9)	<0.001
Chronic kidney disease	156(17.1)	93(57.1)	<0.001
COPD	57(6.2)	29(17.8)	<0.001
Initial laboratory results, Median (q1-q3)			
White Blood Cell ($x10^3/\mu L$)	6.2 (4.8-8.0)	8.1 (5.6-11.1)	<0.001
Hemoglobin (g/dL)	13.1 (12.0-14.2)	12.0 (10.8-13.0)	<0.001
Platelet ($x10^3/\mu L$)	211.0 (167.0-270.0)	184.0 (145.0-245.0)	<0.001
NLR	3.5 (2.4-5.2)	8.0 (5.0-11.0)	<0.001
Glucose (mg/dL)	124.0 (111.0-158.0)	163.0 (127.0-248.0)	<0.001
AST (U/L)	40.0 (32.0-52.0)	66.0 (45.0-89.0)	<0.001
ALT (U/L)	32.0 (23.0-45.0)	47.0 (35.0-70.0)	<0.001
eGFR ($ml/dk/1,73m^2$)	83.0 (67.0-98.0)	56.0 (36.5-75.6)	<0.001
BUN (mg/dL)	32.0 (25.0-41.0)	60,0 (45.0-85.0)	<0.001
Creatinine (mg/dL)	0.9 (0.8-1.0)	1.2 (0.9-1.7)	<0.001
BUN/Creatinine	16.9 (14,5-19.6)	21.5 (18.9-27.6)	<0.001
CRP (mg/L)	55.0 (30.0-100.0)	130.0 (88.0-185.0)	<0.001
Ferritin (mcg/L)	300.0 (167.0-490.0)	650.0 (345.0-953.0)	<0.001
D-dimer (mcg/mL)	0.7 (0.5-1.1)	1.4 (0.9-2.4)	<0.001
Fibrinogen (mg/dL)	450.0 (347.0-543.0)	519.0 (450.0-600.0)	<0.001
Troponin I (ng/mL)	0.1 (0.0-0.1)	0.2 (0.1-0.6)	<0.001
Creatine Kinase MB (ng/mL)	1.0 (0.9-2.0)	4.0 (3.0-6.0)	<0.001

TIA: transient ischemic attack; COPD: Chronic obstructive pulmonary disease; NLR: Neutrophil to lymphocyte ratio; AST: Aspartate aminotransferase; ALT: Alanine Aminotransferase; eGFR: Estimated glomerular filtration rate; BUN: Blood Urea Nitrogen; CRP: C-reactive protein

The stepwise logistic regression models in Table 1, which include all laboratory values not used in $R_2CHA_2DS_2VASc$ scoring, attempted to identify the most important factors explaining mortality. In these models, there were 3 variables other than $R_2CHA_2DS_2VASc$ in the model with the highest mortality explanation rate, and other criteria were excluded from the model because they decreased the model's mortality explanation rate. The C-reactive protein (CRP), aspartate aminotransferase (AST), and neutrophil-to-lymphocyte ratio (NLR) were found to be associated with mortality (Table 2). A new scoring system was created by adding these three new laboratory values associated with mortality to the current scoring system (Table 3). The CAN-$R_2CHA_2DS_2VASc$ score was established by assigning letter C for C-reactive protein (CRP), letter A for aspartate aminotransferase (AST), and letter N for neutrophil to lymphocyte ratio (NLR) (Table 3).

Table 2. Regression analysis of the predictive model for COVID-19 patients (CAN-$R_2CHA_2DS_2VASc$)

Predictive Model	OR (95%CI)	p
$R_2CHA_2DS_2VASc$	1.901 (1.686-2.144)	<0.001
NLR	1.207 (1.131-1.289)	<0.001
AST	1.009 (1.006-1.013)	<0.001
CRP	1.020 (1.014-1.027)	<0.001

Model fit: p < 0,001; Cox & Snell R^2= 0,3051; Nagelkerke R^2= 0,5326; Accuracy=90%

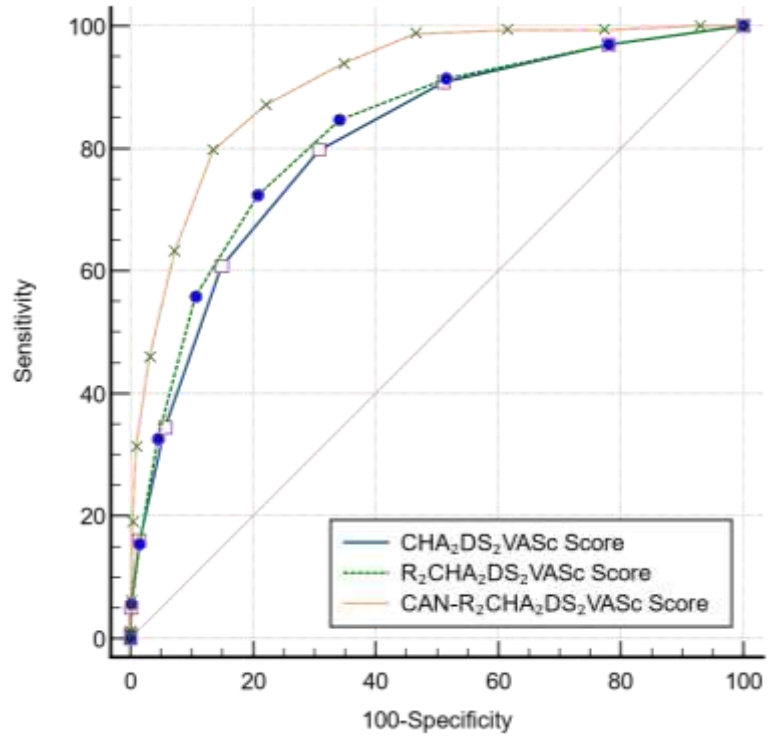
Table 3. Criteria of CAN-$R_2CHA_2DS_2VASc$

Criteria	Category	Points
Congestive heart failure history		+1
Hypertension history		+1
Age	<65 years old	0
	65-74 years old	+1
	≥75 years old	+2
Diabetes mellitus history		+1
Previous stroke, transient ischemic attack, thromboembolism history		+2
Vascular disease history (prior myocardial infarction, peripheral artery disease, or aortic plaque)		+1
Sex	Female	0
	Male	+1
Renal Function (estimated glomerular filtration rate (eGFR)) (ml/dk/1,73m^2)	> 60	0
	30-60	+1
	<30	+2
CRP (mg/L)	<10	0
	10-100	+1
	>100	+2
AST (U/L)	<40	0
	40-80	+1
	>80	+2
NLR	<6	0
	6-9	+1
	>9	+2

AST: Aspartate aminotransferase; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; NLR: Neutrophil to lymphocyte ratio;

ROC curves of CHA_2DS_2VASc, $R_2CHA_2DS_2VASc$, and CAN-$R_2CHA_2DS_2VASc$ scores were analyzed (Figure 1). The area under the curve (AUC) was calculated as 0.810 for CHA_2DS_2VASc, 0.824 for $R_2CHA_2DS_2VASc$, and 0.909 for CAN-$R_2CHA_2DS_2VASc$. The Delong test was used for the comparison of the ROC curve. The AUC of the $R_2CHA_2DS_2VASc$ score was significantly higher than the CHA_2DS_2VASc score (p=0.009).

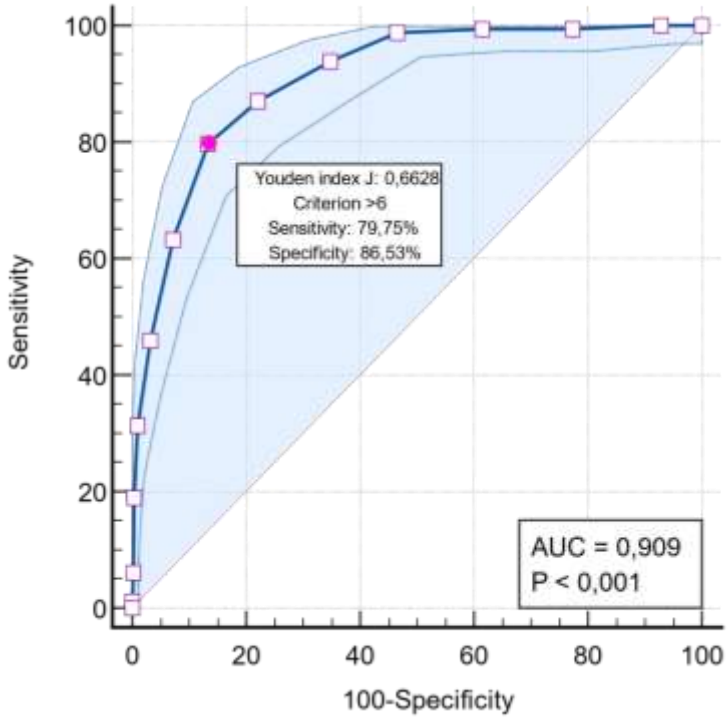
The AUC of the CAN-$R_2CHA_2DS_2VASc$ score was significantly higher than the AUC of both $R_2CHA_2DS_2VASc$ and CHA_2DS_2VASc scores (p<0.001). The point of criterion at which sensitivity and specificity were optimal was selected using the Youden index. The CAN-$R_2CHA_2DS_2VASc$ score sensitivity was 79.8%, specificity was 86.5%, +LR was 5.92, -LR was 0.23, while the criterion was >6 points (Figure 2).



Scores	AUC¥	95% CI	$R_2CHA_2DS_2VASc$	CAN-$R_2CHA_2DS_2VASc$
CHA_2DS_2VASC	0.810	0.785 - 0.833	z= 2.623 **p= 0.009***	z= 7.599 **p< 0,001***
$R_2CHA_2DS_2VASC$	0.824	0.800 - 0.847		z= 6.954 **p< 0,001***
CAN-$R_2CHA_2DS_2VASC$	0.909	0.890 - 0.925		

¥ p<0.001; *DeLong test used for comparison.

Figure 1. Comparison of Scores' ROC curves for survivors.



Statistic	Value	95% CI
Sensitivity	79.75%	72.76% to 85.64%
Specificity	86.53%	84.14% to 88.68%
Positive Likelihood Ratio	5.92	4.94 to 7.10
Negative Likelihood Ratio	0.23	0.17 to 0.32

Figure 2. ROC curve of the CAN-$R_2CHA_2DS_2VASc$ scores, sensitivity, specificity, and criterion.

DISCUSSION

Although COVID-19 was initially thought to be primarily a respiratory disease, evidence suggests that the primary and perhaps most important target of the virus is the endothelium. Endothelial dysfunction is believed to play an important role in the pathogenesis of thromboembolic events in COVID-19.(8, 9) COVID-19 has been suggested to induce a process known as immunothrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade, leading to the formation of intravascular clots in small and larger vessels (10, 11). Endothelial hemostasis plays a vital role in the regulation of fibrinolysis and vessel wall permeability, and its dysfunction triggers immunothrombosis (10, 11, 28). Endothelial dysfunction is associated with atherosclerotic risk factors such as diabetes mellitus, hypertension, hyperlipidemia, inflammation, coronary artery disease, and peripheral artery disease (29, 30). Comorbidities such as diabetes mellitus, hypertension, and cardiovascular disease associated with endothelial dysfunction have been found to be more common in hospitalized patients with COVID-19. These comorbidities have also been observed to be associated with a predisposition to severe COVID-19 and an increased risk of death (31-33).

The CHA_2DS_2VASc score and $R_2CHA_2DS_2VASc$ score, which is formed by including the estimated glomerular filtration rate (eGFR), are simple scoring systems that are commonly used to predict the risk of systemic thromboembolism in patients with AF (10, 11). These scores are primarily designed to predict the risk of thrombosis, and many of their components are also prognostic risk factors for COVID-19. As the patients' CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ scores increase, their susceptibility to endothelial dysfunction and thrombosis increases. Since endothelial dysfunction and thrombosis play an important role in the pathogenesis of COVID-19, these scores were thought to predict in-hospital mortality in this patient population (9, 10). Studies have shown that in COVID-19 patients, the CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ obtained by scoring the male sex predicts in-hospital mortality (16-18, 21).

This study supports previous studies. Both the CHA_2DS_2VASc and $R_2CHA_2DS_2VASc$ scores demonstrated increased in-hospital mortality. Some studies have shown that renal dysfunction is associated with increased morbidity and mortality in COVID-19 (19, 20). In light of these studies, we investigated whether the $R_2CHA_2DS_2VASc$ score, which was created by including eGFR in the CHA_2DS_2VASc score, was superior in predicting mortality, since kidney functions are an important cause of mortality in this population of patients. As a result, the $R_2CHA_2DS_2VASc$ score was superior to the CHA_2DS_2VASc score in terms of mortality prediction.

Since COVID-19 is a systemic infectious disease, it causes destruction and increases cell inflammation. Therefore, it is not surprising that the CRP, AST, and NLR values increase in COVID-19 patients. Studies have shown that inflammatory markers such as CRP and NLR are associated with increased mortality in COVID-19 (34-37). Significant increases in AST have also been reported in COVID-19 patients. The increase in AST, which is found not only in the liver but also in many organs, can be explained by the resulting multiorgan dysfunction (38-40). In the model created with the CRP, AST, and NLR values added to the $R_2CHA_2DS_2VASc$ score, and it was possible to evaluate endothelial dysfunction and thrombosis together with cell destruction and inflammation parameters.

Consequently, early estimation of the risk of death in COVID-19 patients is of great importance in terms of clinical patient management and treatment strategies, and we found that the ability of the CAN-$R_2CHA_2DS_2VASc$ score to predict mortality is better than the $R_2CHA_2DS_2VASc$ and CHA_2DS_2VASc scores. *The CAN-$R_2CHA_2DS_2VASc$ score we defined had sufficient sensitivity and specificity and was more successful in predicting mortality.* Unlike other scores, it includes both clinical and laboratory parameters, making it a strong prognostic indicator.

This study has some limitations. First, this study is a retrospective and single-center study. This may limit the generalizability of this study's findings. Furthermore, this study was carried out in the early period of the pandemic, when variants of COVID-19 (delta, omicron, etc.) had not yet emerged and vaccination had not started in Türkiye. Different viral strains and vaccination status can influence the risk of complications and prognosis among infected patients. The performance of this new scoring system may differ between currently infected patients with different viral strains and vaccination status. Due to increased vaccinations and newly emerging variants, the efficacy of this model must be tested in a population of new dominant variants. Racial differences may also affect the severity and prognosis. The generalizability of the results and the usability of the score in clinical practice should be evaluated with larger studies.

CONCLUSION

The results of this study showed that the CAN-$R_2CHA_2DS_2VASc$s score could be useful in predicting in-hospital mortality in patients with COVID-19. Furthermore, the predictive ability of CAN-$R_2CHA_2DS_2VASc$ was better than the $R_2CHA_2DS_2VASc$ and CHA_2DS_2VASc scores to predict mortality in this patient population. Since it is an easily calculable score, it can help determine clinical patient management and treatment strategies by estimating the risk of mortality early.

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RESEARCH ARTICLE

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Investigation of the Relationship of Two-Glass Test with Prostate Biopsy and Presence and Grade of Asymptomatic Prostate Inflammation in Men with Serum Prostate-Specific Antigen Level Between 2.5-10 ng/ml

ABSTRACT

Objective: Prostate-specific antigen (PSA) is utilized as a marker to detect prostate cancer. Elevated PSA levels often lead to prostate biopsy to assess the potential presence of cancer. However, PSA elevation is not specific to cancer and can be caused by various conditions, including benign prostatic hyperplasia (BPH), urinary tract infections, and chronic prostatitis. Notably, approximately 66% of patients undergoing biopsy do not have prostate cancer, leading to unnecessary procedures and associated complications. Chronic prostatitis is detected in around 40% of these biopsies. The two-glass test involves examining urine before and after a rectal examination to diagnose chronic prostatitis. This study aims to investigate the effectiveness of the two-glass test in predicting prostatitis and inflammation in patients with PSA levels between 2.5-10 ng/ml who have undergone prostate needle biopsy.

Materials and Methods: The study included fifty-two male patients aged between 50 and 78 years with PSA levels between 2.5 and 10 ng/ml who presented to our clinic. All patients underwent the EPS-two-glass test and prostate biopsy. EPS (expressed prostatic secretion) is obtained by collecting fluid from the urethra after prostate massage, while VB-3 (voided bladder-3) is urine collected after a massage. These samples are used to detect prostate infection. Prostate inflammation was deemed significant if ≥10 leukocytes were observed under the microscope. Patients were categorized into three groups based on pathology results: prostate cancer, BPH, and chronic prostatitis. The chronic prostatitis group was further classified based on histopathological calcification described by Nickel.

Results: Chronic prostatitis was detected in 38% of the study participants. VB3 positivity was significantly higher in the chronic prostatitis group compared to the other groups (p = 0.028). Although no significant difference was observed in the prevalence of inflammation and PSA elevation, PSA levels were higher in the multifocal inflammation subgroup compared to the focal inflammation group.

Conclusions: The relationship between chronic prostatitis and PSA elevation remains unclear. Although this study did not find a statistical relationship between inflammation and PSA elevation, the significant correlation between chronic prostatitis and VB3 positivity suggests a potential link. These findings can serve as a foundation for further research aimed at reducing unnecessary biopsies.

Keywords: PSA Elevation, Prostate Cancer, Chronic Prostatitis, Two Glass Test.

Serum Prostat-Spesifik Antijen Düzeyi 2,5-10 ng/ml Arasındaki Erkeklerde İki Kadeh Testinin Prostat Biyopsisi Ve Asemptomatik Prostat İnflamasyonu Varlığı ve Derecesiyle İlişkisinin Araştırılması

ÖZET

Amaç: Prostat spesifik antijen (PSA), prostat kanserini tespit etmek için kullanılan bir belirteçtir. Yüksek PSA değerlerinin tespit edilmesi durumunda, prostat kanseri olasılığı göz önünde bulundurularak prostat biyopsisi yapılır. PSA yükselmesi prostat kanserine özgü olmayabilir, aynı zamanda benign prostat hiperplazisi (BPH), idrar yolu enfeksiyonu ve kronik prostatit gibi durumlar da neden olabilir. Biyopsiye giren hastaların yaklaşık %66'sında prostat kanseri tespit edilmez ve hastalar gereksiz biyopsi ve biyopsi komplikasyonlarına maruz kalırlar. Bu biyopsilerin yaklaşık %40'ında kronik prostatit tespit edilir. İki bardak testi, kronik prostatiti teşhis etmede kullanılan rektal muayene öncesi ve sonrası idrarın incelenmesine dayanır. Bu çalışmada, 2,5-10 ng/ml arasında PSA değerine sahip ve prostat iğne biyopsisi yapılan hastalarda iki bardak testinin prostatit ve inflamasyon insidansını tahmin etmedeki etkinliğini ortaya çıkarmayı amaçladık.

Gereç ve Yöntem: Kliniğimize başvuran, yaşları 50 ile 78 arasında değişen, PSA değerleri 2,5 ile 10 ng/ml arasında olan elli iki erkek hasta çalışmaya dahil edildi. Tüm hastalara EPS-iki bardak testi ve prostat biyopsisi uygulandı. EPS; prostat masajı yapıldıktan sonra üretradan sıvı alınarak elde edilen bir örnektir; VB-3; masaj sonrası boşaltılan yaklaşık 10 ml idrarı gösterir. EPS ve VB3 prostat enfeksiyonunu tespit eder. Mikroskop altında ≥10 lökosit, prostat inflamasyonu için anlamlı kabul edildi. Patoloji sonuçlarına göre, hastalar üç gruba ayrıldı; prostat kanseri, BPH ve kronik prostatit. Kronik prostatit grubu, Nickel tarafından tanımlanan histopatolojik kalsifikasyona göre sınıflandırıldı.

Bulgular: Bu çalışmada, kronik prostatit oranının %38 olduğu bulundu. VB3 pozitifliği, kronik prostatit grubunda diğer gruplara göre istatistiksel olarak önemli bulundu (p = 0,028). İnflamasyon prevalansı ile PSA yükselmesi arasında istatistiksel olarak anlamlı bir fark bulunmamakla birlikte, PSA, multifokal inflamasyon alt grubunda, odaklı inflamasyon hastalar grubundan daha yüksek bulundu.

Sonuç: Kronik prostatit ile PSA yükselmesi arasındaki ilişki hala belirsizdir. Bu çalışmada, inflamasyon ile PSA yükselmesi arasında istatistiksel bir ilişki bulunmamış olmasına rağmen, kronik prostatit ile VB3 pozitifliği arasındaki önemli korelasyon, bu ilişkinin olasılığını güçlendirmektedir. Bu bulgular, gereksiz biyopsileri önlemeye yönelik ileri çalışmaların temeli olabilir.

Anahtar Kelimeler: PSA Yüksekliği, Prostat Kanseri, Kronik Prostatit, İki Kadeh Testi.

INTRODUCTION

Prostate-specific antigen (PSA) is a commonly used marker for detecting and monitoring prostate cancer (1,2). However, PSA levels can also be elevated in various physiological events and benign conditions, leading to challenges in its specificity for cancer detection. Procedures such as prostate massage, transrectal ultrasonography (TRUS), and biopsy can temporarily increase PSA levels (3-5). While additional tests like the free PSA/total PSA ratio, PSA density, and Multiparametric Prostate Magnetic Resonance Imaging (MpMRI) have been used to enhance PSA test specificity, rates of unnecessary biopsies remain high (6). Spontaneous fluctuations in PSA levels without apparent cause are considered a potential cause of false-positive results. However, the relationship between the magnitude of these fluctuations and prostate histology is not well understood. The association between serum PSA levels and subclinical prostatic inflammation is also unclear. Elevated PSA levels in patients with negative biopsy results present a challenge for clinicians in explaining the PSA elevation in prostate cancer screening (7,8).

Inflammation may be present in up to 42% of patients undergoing prostate biopsy (7). High serum PSA levels are often linked to prostate inflammation, contributing to false-positive PSA tests. However, there is limited guidance on how to address this inflammation-related confusion when deciding on biopsy. Besides non-malignant conditions, benign prostatic hyperplasia (BPH) and prostatitis have been reported to contribute to PSA elevation. Studies investigating the relationship between PSA levels and asymptomatic prostatic inflammation based on morphological parameters have yielded conflicting results.

Current knowledge about prostatic inflammation in biopsies primarily stems from retrospective studies. Our study aimed to assess the frequency of asymptomatic prostatitis in prostate needle biopsy specimens from men with PSA levels between 2.5-10 ng/ml and evaluate the predictive value of the two-glass test for detecting this inflammation.

Prostate-specific antigen (PSA) is a widely used marker in the detection and follow-up

of prostate cancer (1,2). PSA is not specific to cancer; its level can be elevated in many physiological events and benign conditions (3,4,5). Various urological manipulations, prostate massage, transrectal ultrasonography (TRUS), and biopsy cause a temporary increase in serum PSA value. Although some auxiliary applications such as free PSA/total PSA ratio, PSA density, and Multiparametric Prostate Magnetic Resonance (MpMRI) imaging, which have been popular in recent years, are used to increase the specificity of the PSA test, unnecessary biopsy rates are still high (6). Many researchers consider spontaneous changes in the PSA level that occur for no apparent reason as one of the causes of false positive results. However, the relationship between the magnitude of spontaneous fluctuations in PSA value and prostate histology is not yet well known. The relationship between serum PSA value and subclinical prostatic inflammation is still unclear. Elevated PSA levels and negative biopsy results in patients with abnormal rectal examination make it difficult for clinicians to explain this increase in prostate cancer screening (7,8). Inflammation may be present in 42% of patients undergoing prostate biopsy (7). In most patients, high serum PSA levels are associated with prostate inflammation, which is considered one reason for false positive PSA testing. There is not enough information about how to eliminate this confusion caused by inflammation when making a biopsy decision. Apart from non-malignant conditions, BPH (1) and prostatitis have been reported to contribute to PSA elevation (4,7). Many studies have based the relationship between PSA value and asymptomatic prostatic inflammation on morphological parameters (1-3). These gave contradictory results.

Current information on prostatic inflammation in biopsy is largely based on retrospective studies (9). Our aim in this study was to investigate the frequency of asymptomatic prostatitis in prostate needle biopsy specimens in men with a PSA value between 2.5-10 ng/ml and the predictive power of the two-glass test for this inflammation.

MATERIAL AND METHODS

Between June 2004 and August 2005, patients presenting to the urology outpatient clinic with lower urinary tract complaints and serum PSA values between 2.5 and 10 were eligible for inclusion in the study. The study received approval from the ethics committee. All patients underwent a series of tests, including rectal examination, full urine examination, urine culture, expressed prostatic secretion (EPS), and the two-glass test. EPS, obtained by collecting fluid from the urethra after a prostate massage, and VB-3 in the two-glass test, referring to the first 10 ml urine sample after prostate massage, were analyzed. Additionally, 8-quadrant prostate biopsy and prostate volume measurement were performed under TRUS guidance.

Patients were excluded from the study if they:

1) Had symptoms of prostatitis
2) Had a PSA value less than 2.5ng/ml or more than 10ng/ml
3) Had a history of prostate-related surgery
4) Used drugs that affect PSA
5) Had a history of rectal ultrasound probe insertion
6) Had a urinary tract infection

Urine samples were collected before and after prostate massage, centrifuged, and the amount

of leukocytes in the sediment was measured. Prostate inflammation was considered significant if it was ≥10 leukocytes at high magnification under the microscope. PSA levels and prostate volumes were determined by transrectal ultrasound. All patients underwent 8-quadrant 18 auge needle fine aspiration biopsy. Patients diagnosed with chronic prostatitis in the biopsy sample were classified according to the histopathological classification of chronic prostatitis specified by Nickel (Tables 1a, 1b, and 1c) based on localization, extent, and degree. Thirteen out of 65 initially included patients were excluded based on the exclusion criteria, leaving 52 patients for the study.

Table 1a. Classification according to localization and histological features.

Anatomical Localization	Histological Pattern
Glandular	Inflammatory content in the duct or epithelium and/or in the lumen
Peri glandular	Inflammatory content in the stroma gland and distance to the channels is within 50μm
Stromal	The inflammatory content is in the stroma, and the gland and the distance to the channels are 50μm further.

Table 1b. Classification according to spread and area invaded by inflammatory cells.

According to the spread	Area invaded by inflammatory cells
focal	less than 10%
multifocal	10-50%
Widespread	more than 50%

Table 1c. Classification according to grade and morphology

Grade (degree)	Morphological description (inflammatory cell density, cell/mm²)
1/light	Inflammatory cells separated by distinct spaces (< 100)
2/medium	Tissue destruction and inflammatory cell clusters without lymphoid nodules. (100-500)
3/severe	Tissue destruction and inflammation cell clusters with lymphoid nodules (>500)

Statistical Analysis: The statistical analysis of the study was performed using the SPSS (Statistical Package for Social Sciences) version 10.0 for Windows. Student's t-test and One-way ANOVA test were employed to compare numerical data, in addition to descriptive statistical methods. Kruskal-Wallis and Mann-Whitney U tests were utilized for comparing groups with different distributions. The chi-square test was applied for the qualitative comparison of groups. The data were considered statistically significant at a 95% confidence interval with $p<0.05$.

RESULTS

The mean age of the cases was 65 ± 7 years. There was no statistically significant difference between the groups in terms of patient age, total PSA, free PSA levels, PSAD, f/tpsa prostate volume and postvoid residual amount ($p>0.05$).

Considering the VB3 positivity rates (Table 2 and Figure 1), the elevation in the chronic prostatitis group was statistically significant compared to the other groups.

Table 2. Table of VB3 positivity in group

		Chronic Prostatitis	BPH	Prostate Cancer	p
		%	% (n)	% (n)	
VB3	+	40.0 (8)	5.0 (1)	20.0 (2)	*0.028
	-	60.0 (12)	95.0 (19)	80.0 (8)	

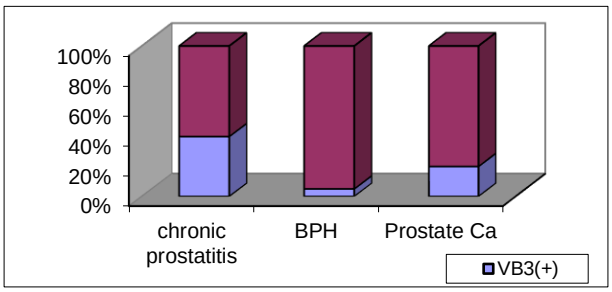

Figure 1. VB3 distribution by groups.

The mean age of the cases with a PSA value ≤4 was significantly lower than that of the cases with a PSA level of >4. No significant difference was found between prostate volume and PSA levels ($p>0.05$). Also, there is no statistically significant difference between PSA and histopathologic classification in the chronic prostatitis group (Table 3). According to VB3 positivity, no statistically significant difference was found between the mean PSA levels of the cases, the distribution of

inflammation localization, and the spread of inflammation (p>0.05) (Table 4). There is no statistically significant relationship between the prevalence of inflammation, localization of inflammation, grade of inflammation and age groups, PV level, and PSA level (p>0.05) (Table 5).

Table 3. Comparison of PSA level with histopathologic classification in the chronic prostatitis group.

		PSA				*p*
		≤ 4		> 4		
		Mean±SD	Median	Mean±SD	Median	
Age		58.00±7.35	56.5	67.06±6.83	67.5	***p:0.033****
Prostate Volume (PV)		42.50±7.32	40.5	66.56±44.67	60.5	***p:0.185***
		N	**%**	**n**	**%**	
Localization of inflammation	**stromal**	2	50.0	4	28.6	***p:0.569***
	glandular+ periglandular	2	50.0	10	71.4	
Prevalence of inflammation	**focal**	3	75.0	5	35.7	***p:0.275***
	multifocal	one	25.0	9	64.3	
Grade	**I**	2	50.0	6	42.9	***p:1.000***
	II+III	2	50.0	8	57.1	

Table 4. Table showing the comparison of chronic prostatitis features and VB3 results

		VB3				*p*
		+		-		
		Mean±SD	Media	Mean±SD	Media	
PSA		6.54±1.82	5.72	5.88±1.97	5.80	***0.32***
		n	**%**	**n**	**%**	
Localization of Inflammation	**stromal**	2	33.3	4	33.3	***1.00***
	glandular+ periglandular	4	66.7	8	66.7	
Prevalence of Inflammation	**focal**	1	16.7	7	58.3	***0.152***
	multifocal	5	83.3	5	41.7	
Grade of Inflammation	**I**	2	33.3	6	50.0	***0.638***
	II+III	4	66.7	6	50.0	

Table 5. Patient characteristics according to the prevalance, localization and the grade of inflammation

		Prevalence of Inflammation			Localization of Inflammation			*Grade of Inflammation*		
		Focal	Multifocal	*p*	Stromal	Glandular+ Periglandular	*p*	I	II+III	*p*
		%	%		%	%		%	%	
Age	**< 60**	37.5	10.0	***p:0.275***	16.7	25.0	***p:1.000***	25.0	20.0	***p:1.000***
	≥ 60	62.5	90.0		83.3	75.0		75.0	80.0	
PV	**<50**	62.5	40.0	***p:0.637***	16.7	66.7	***p:0.131***	50.0	50.0	***p:1.000***
	> 50	37.5	60.0		83.3	33.3		50.0	50.0	
PSA	**≤ 4**	37.5	10.0	***p:0.275***	33.3	16.7	***p:0.569***	25.0	20.0	***p:1.000***
	> 4	62.5	90.0		66.7	83.3		75.0	80.0	

While there was no statistically significant difference in serum PSA mean and PSA density between cases with stromal inflammation localization, the FPSA ratio was found to be at a statistically significant level (p<0.05). (Table 6)

Table 6. Comparison of serum PSA, PSA density and FPSA percentage by inflammation localization

	Inflammation Localization				*p*
	Stromal		Glandular+ Periglandular		
	Mean±S	Median	Mean±S	Median	
Serum PSA	5.82±2.5	5.59	5.74±1.76	5.52	***p:1.000***
PSA Density	0.09±0.0	0.08	0.13±0.08	0.11	***p:0.779***
FPSA rate	26.11±9.6	25.19	17.98±6.48	18.84	***p:0.039****

DISCUSSION

Asymptomatic prostate inflammation is considered one of the subgroups of chronic prostatitis, typically diagnosed through EPS/glass test or histopathological evaluation. While PSA measurement is crucial for early prostate cancer diagnosis, its sensitivity and specificity are limited. In asymptomatic patients with high PSA values, approximately 50% of cases might be attributed to prostatitis, as detectable after TRUS biopsy, suggesting a potential association between high

PSA values and inflammation (11,12). However, some studies argue against a significant increase in PSA levels due to chronic prostatitis (13,14). In our study, we observed a prostatitis rate of 38% post-prostate biopsy, consistent with reported rates in the literature ranging from 5-98% in various biopsy methods and autopsy specimens (15,16). Brawn et al. reported chronic prostatitis in 50% of 105 autopsy samples in their study (17).

A notable finding in our study was the significantly higher VB3 positivity in the chronic prostatitis group compared to other groups ($p = 0.028$). In one study, VB3 positivity was detected in 92% of those with positive EPS results. Of the 180 patients who had less than 10 leukocytes in EPS, 178 of them also had less than 10 leukocytes in the VB3 test (18). This indicates that VB3, which can be easily obtained from all patients, could potentially replace EPS, which is sometimes unavailable. Lee et al. reported a 20.7% prostate cancer detection rate in patients with negative EPS or VB3 tests, suggesting a potential role for these tests in identifying patients at higher risk for prostate cancer (19). Additionally, in a systematic review, antibiotic treatment normalized PSA levels in a significant number of patients with positive VB3 or EPS tests, indicating a potential benefit of antibiotic therapy with quinolone treatment in symptomatic VB3-positive patients (20).

While some studies have found a positive correlation between prostate volume and PSA levels, we did not observe a significant relationship in our study. The discrepancy may be due to differences in sample size, prostate volume variability, and the PSA range studied. Notably, both our study and another study of Kwak et.al observed a positive correlation between inflammation extent and prostate volume, suggesting a potential link between prostate inflammation and hyperplasia (21). While multifocal inflammation was 60% in those with PV >50cc, it was found around 40% in those with <50cc in our study.

No significant relationships were found between age groups, prostate volume, PSA levels, and inflammation localization in our study. However, glandular and peri-glandular inflammation predominated in prostates below 50cc, while stromal inflammation was more prominent in larger prostates (>50cc), reflecting the shift in glandular to stromal tissue ratio with increasing prostate size. This finding warrants further investigation. In the study of Nadler et al., it was noted that both acute and chronic inflammation caused an increase in PSA. They reported acute inflammation in 63% of patients with elevated PSA and 27% of patients with normal PSA. For chronic inflammation, these values are 99% and 77%, respectively ($p = 0.05$) (22). Neal found an increase in PSA after acute inflammation induction in his study in monkeys and noted that PSA decreased to its normal value with its treatment (7). Although it has been shown in many studies that BPH increases PSA levels, this was not taken into account in some studies advocating the relationship between PSA elevation and chronic inflammation (23,24).

Biopsying patients with high PSA levels but negative for cancer does not definitively rule out undetected microscopic prostate cancer. Chronic inflammation may occur in atrophic glandular areas, where PSA production is diminished, potentially masking inflammation. Studies have presented conflicting findings regarding the correlation between inflammation and PSA levels (25). The free-to-total PSA ratio (f/tPSA) is significantly higher in stromal inflammation compared to other regions ($p = 0.039$). This elevation may be due to the breakdown of the anatomical and physiological barrier between the prostate and blood vessels in the stromal region, which is rich in blood vessels. Moon's study, which infected the human prostate carcinoma cell line LNCaP with in vitro bacteria, did not find an increase in PSA levels (26). This result supports the hypothesis that infection and inflammation may facilitate the diffusion of PSA into the blood by affecting natural physiological and anatomical barriers.

In our study, we observed a relationship between the spread of inflammation and PSA elevation, although it was not statistically significant. The mean PSA was higher in the multifocal inflammation subgroup compared to the focal inflammation group.

These findings suggest that while inflammation and PSA levels may be related, the exact nature of this relationship and its clinical implications require further investigation.

The most important limitation is the limited number of patients. Further multicentre study should be carried out to establish a more accurate model. Another limiting factor is that the prostate biopsy was performed in 8 quadrants instead of 12 quadrants. In conclusion, our study contributes to the understanding of asymptomatic chronic prostatitis and its relationship with PSA elevation. While we did not find a statistical association between inflammation and PSA elevation, we observed a significant correlation between chronic prostatitis and VB3 positivity. These findings suggest a potential role for VB3 in identifying patients at higher risk for prostate cancer and highlight the need for further multicenter studies to establish more accurate models.

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RESEARCH ARTICLE

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COVID-19 Awarenessscale (Cas) Turkish Form: A Validity and Reliability Study

ABSTRACT

Objective: In this study, we aimed to develop a valid and reliable scale to measure the level of awareness of people about COVID-19.

Materials and Methods: A total of 244 people participated in the research. The item pool was created in line with the literature and expert opinions. The prepared items were examined by four experts in terms of content validity, language, and expression, and a 28-item scale form was created. Following these stages, the first form consisting of 28 items was applied to 29 people as a pilot study. Explanatory and confirmatory factor analyses were employed to test the construct validity.

Results: As a result of the explanatory factor analysis, it was determined that the scale consisted of 15 items and 3 sub-dimensions. These sub-dimensions were respectively named "Protection", "Knowledge of COVID", and "Effort to Obtain Information". When the fit indices obtained from the confirmatory factor analysis results were examined, we saw that the three-factor scale construct had a high fit at an acceptable level.

Conclusions: Based on the data obtained from this study, we concluded that the COVID-19 awareness scale was valid and reliable to evaluate the awareness level of people. The COVID-19 awareness scale we have devised can be employed by researchers who seek to measure individuals' awareness levels regarding a pandemic similar to COVID-19.

Keywords: Awareness, COVID-19, Validity, Reliability, Scale.

COVİD-19 Farkındalık Ölçeği (CAS)Türkçe Formu: Geçerlik Ve Güvenirlik Çalışması

ÖZET

Amaç: Bu çalışmada, insanların COVİD-19 hakkındaki farkındalık düzeylerini ölçecek geçerli ve güvenilir bir ölçeğin geliştirilmesi amaçlanmaktadır.

Gereç ve Yöntem: Araştırmaya toplam 244 kişi katılmıştır. Madde havuzu literatür ve uzman görüşleri doğrultusunda oluşturulmuştur. Hazırlanan maddeler dört uzman tarafından kapsam geçerliliği, dil ve anlatım açısından incelenerek 28 maddelik bir ölçek formu oluşturulmuştur. Bu aşamaların ardından 28 maddeden oluşan ilk form 29 kişiye pilot çalışma olarak uygulanmıştır. Yapı geçerliliğini test etmek için açıklayıcı ve doğrulayıcı faktör analizleri kullanılmıştır.

Bulgular: Açımlayıcı faktör analizi sonucunda ölçeğin 15 madde ve 3 alt boyuttan oluştuğu belirlenmiştir. Bu alt boyutlar sırasıyla "Korunma", "COVID Bilgisi" ve "Bilgi Edinme Çabası" olarak adlandırılmıştır. Doğrulayıcı faktör analizi sonuçlarından elde edilen uyum indeksleri incelendiğinde üç faktörlü ölçek yapısının kabul edilebilir düzeyde yüksek bir uyuma sahip olduğu görülmüştür.

Sonuç: Bu çalışmadan elde edilen verilere dayanılarak, COVID-19 farkındalık ölçeğinin kişilerin farkındalık düzeyini değerlendirmede geçerli ve güvenilir olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Farkındalık, COVID-19, Geçerlilik, Güvenilirlik, Ölçek.

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INTRODUCTION

The COVID-19 pandemic, which started in 2019 in the city of Wuhan, China and spread all over the world in a short time, continues to be a problem, affecting almost all parameters of social life, especially the socioeconomic and sociocultural ones. Much important topics such as health, education, economy, tourism, trade, digitalization, culture, and technology can be counted among these parameters. Leading health institutions in the world, especially the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC), have shared the current data obtained about the coronavirus disease (number of cases, number of recovered, number of deceased, etc.) over their official websites with the public. We can assert that the introduction of the disease by national and international health authorities in the light of scientific data, effective communication, and interaction with the public in terms of effective fight against the disease and ways to prevent the disease are very important in terms of informing the public correctly.

The transition to vaccination, as a result of intense efforts shown during the COVID-19 pandemic process, has been an important step in the fight against the disease. However, when the latest data shared by the health authorities about the disease are evaluated, we can state that the disease continues to be a current problem in terms of the number of cases, especially the number of deaths.

As a matter of fact, the information shared by the World Health Organization (WHO) on its official website regarding the disease on February 21, 2022, is remarkable. In the data shared about the disease, it is seen that the total number of cases worldwide is 423,437,674, while the total number of deaths is 5,878,328 and the number of new cases in the last 24 hours is 1,248,920 (1). In the light of these data, we can state that the COVID-19 pandemic is still a current issue. Therefore, in this study, we aimed to develop a scale to reveal the awareness level of the COVID-19 pandemic in the society regarding its socioeconomic and sociocultural consequences and its effects on almost every aspect of social life, with the prediction that it will go down in history as one of the most important events of the 21st century.

MATERIAL AND METHODS

Creation of the Item Pool: First, a commission was established by the researchers to determine the items. The commission included 1 communication, 1 law, 1 management, and 1 biostatistics expert. After examining the literature regarding the subject, the commission prepared 28 items related to the scale to be developed. The prepared items were examined by four experts in terms of content validity, language, and expression. The experts stated that the prepared items were valid to examine whether an awareness of COVID-19 has been sufficiently formed in the society during the COVID-19 pandemic, adding that some items had to be developed in terms of language and expression. The changes made in line with the suggestions of the experts were finally checked by another person who is an expert in teaching Turkish. After these stages, the first form consisting of 28 items was applied to 29 people as a pilot study. Item analyses, including arithmetic averages of the items, item-total statistics, item discrimination coefficients, were performed on the data obtained because of the pilot application. In line with the item analysis and the suggestions of the researchers, 8 items were removed from the scale and necessary language corrections were made. After these stages, the scale consisting of 20 items was ready for application.

Application of the Scale: The 20-item scale form created by the researchers was applied in a province in the Southeastern Anatolia Region of Turkey using a convenience sampling method. Participants were determined completely randomly, and the scale was applied to a total of 244 participants on a completely voluntary basis. The ethics committee approval of the study was obtained from Siirt University Ethics Committee (Ethics code: 10.09.2021-1165). Then, the researchers took 250 printouts of the scale form. Using these printouts, the scale was applied on a face-to-face basis by the researchers. Since the same answers were checked in all questions in 6 of these forms, they were left out of the evaluation.

Ethics Approval: Approval was obtained from the ethics committee of Siirt University (Ethics code: 10.09.2021-1165). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

Data Analysis: We utilized the Statistical Package for Social Sciences version 29.0 software for Windows (IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp., USA) and AMOS for statistical calculations. For the analysis of the 20 items applied in the scale, the item averages and standard deviations were examined. The arithmetic mean of the item averages was 3.95, while the standard deviation was 0.61. The smallest mean of the items is 3.59 and the largest is 4.29. The differences between the item averages were tested with the Friedman test. According to the Friedman test results, the item averages were found to be similar to each other ($p>.05$). The corrected item total correlation coefficients of the items were also examined. Alpar reported that a correlation coefficient above 0.30 distinguished individuals well, while items between 0.20-0.30 would be taken to the test if deemed necessary, and that items below 0.20 should be removed from the scale (2).

The corrected item total correlation of Item 4 was found 0.15. If Item 4 is removed, Cronbach's alpha coefficient, which gives information about the reliability of the scale, also increases. Based on these results, Item 4 was removed from the scale.

As a result of the comparison of the group averages of the lower and upper 27% (item discrimination power index), another test method for item discrimination, the item discrimination power indices of the items were found to be statistically significant (p<.001). This shows that these items are sufficient to distinguish participants that have high COVID awareness from those with low awareness.

Split-half reliability was also performed for the reliability of the test. As a result of the split-half reliability test, the Spearman-Brown correlation coefficient was found 0.80. This result shows that the reliability of the scale is excellent. Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) were also performed on the 244 scale forms collected by the researchers. While determining the number of factors in the exploratory factor analysis, the fact that the eigenvalues are above 1 and the breaks in the line plot (scree plot) were taken into account. At this stage, Item 4, with a loading value below 0.40, was excluded from the analysis. Similarly, Tsai and Chai also removed items with factor loading values below 0.40 in their scale development study (3). After the removal of these items, the new data consisting of 19 items was retested using 3 factors. Afterwards, it was checked whether there was conceptual integrity between the items divided into 3 factors according to the data set and it was observed that the 3 factors formed consisted of items that were conceptually closely related to each other and could be evaluated under the same group, however, Item 6, Item 7, Item 8, and Item 18 disrupted this conceptual integrity. For this reason, Article 6, Article 7, Article 8, and Article 18 were removed from the scale. The three-factor construct was reanalyzed with the remaining 15 items, and the loads of the items included in each factor were calculated. The 3-factor construct of the remaining 15-item scale was found to be appropriate in terms of factor loadings. Then, the corrected item total correlation of each item with the 15-item scale was examined and it was observed that the correlations of all items were well above 0.20.

Confirmatory factor analysis (CFA) was performed to test the suitability of the three-factor construct, determined as a result of the EFA. Attention was paid to ensure that the CMIN/DF value was less than three in order to accept the accuracy of this construct. Apart from these, CFI, AGFI, GFI, NFI, IFI and TLI fit statistics were employed to evaluate the suitability of the proposed model within the scope of CFA. An RMSEA value below 0.08 was determined as a criterion. It was also decided that GFI, CFI, NFI, NNFI (TLI) and IFI fit indices above 0.90 as stated in the literature would be accepted as a criterion. An AGFI index between 0.85 and 0.90 indicates an acceptable fit, while a range between 0.90 and 1.00 indicates a perfect fit (4-5).

Finally, Cronbach's alpha, McDonald's omega (Ω), construct reliability (CR), and average variance extracted (AVE) coefficients were calculated to test the convergent and divergent validity, internal consistency, and construct reliability of the 15-item scale.

RESULTS

In the scale, 4 demographic characteristics were examined. 50.6%(n=123) of the participants were females, 49.4%(n=120) were males. 79.8%(n=194) of the participants were single. The highest number of participants was in the age range of 18-25 years. 76.5%(n=186) of the participants were university graduates.

First, the Kaiser-Meyer-Olkin (KMO) and Bartlett's Test of Sphericity were conducted to determine whether the data group collected within the scope of the research was suitable for analysis. For the sample to be suitable for explanatory factor analysis, the KMO value should be greater than > 0.5. The fact that the p value of Bartlett's test statistic (chi-square statistic) is less than< 0.05 shows that the correlation matrix is suitable for explanatory factor analysis **(6)**. The KMO value in this analysis was found 0.80. Bartlett's test statistic (chi-square=1020.56, p<.001) also showed that the -data set used was suitable for EFA (7,8,9,10). Following this stage, Varimax rotation and principal component analysis were performed to determine the number of factors that comprised the scale. In examination of the EFA results, we noticed that the scale was divided into three factors with an eigenvalue greater than 1 according to the scree plot (**Fig 1**), 15 items in the scale were also grouped under 3 factors.

The EFA results are given in Table 1 According to Table 1, the eigenvalues of the 3 factors were greater than 1. The eigenvalue of the first factor was 3.76, the second factor was 2.19, and the third factor was 1.680. The variance explained by Factor was 34.08%, while the variance explained by Factor 2 was 20.62% and by Factor 3 16.20%. The total explained variance was 70.90%. When the variances explained by the factors were evaluated for the factors with eigenvalues greater than and the scree plot together, we concluded that the scale consisted of three factors. We also found that the lowest factor loading was 0.54. When the values in the 'corrected item-total correlation' column, which gives the correlation of the items forming the scale with the whole scale, were examined, we observed that the lowest correlation was in Item 5, with a value of 0.43. Thus, the condition that these values should be above 0.20 was met. As a result of explanatory factor analysis,

the scale consisting of 15 items was divided into 3 sub-dimensions. Taking the expressions measured by the items in these sub-dimensions into account, the sub-dimensions were named Protection (Items 14, 9, 12, 11, 19, 13, 15, 10, 17, and 16), Knowledge of COVID (Items 1, 2, and 3) and Effort to Obtain Knowledge (Items 5 and 20) by the researchers.

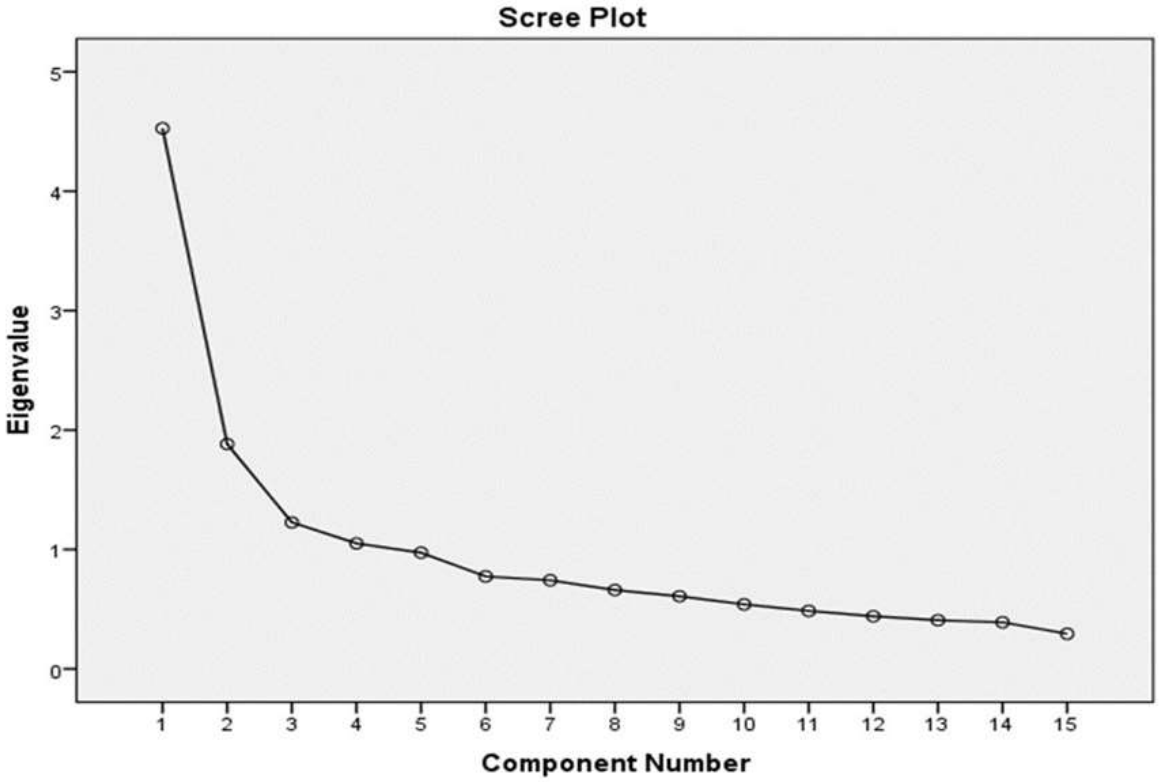

Fig.1. The scree plot of the extracted factors.

Table 1. Exploratory factor analysis of the COVID-19 awareness scale

	Items	New Number	Factor loading	h^2 *	Corrected Item-total Correlation	Eigenvalue	%Variance	Cumulative % Variance
Factor 1 (Protection)	14	1	.68	.72	0.55	3.76	34.08	70.90
	9	2	.67	.49	0.49			
	12	3	.66	.50	0.54			
	11	4	.62	.55	0.48			
	19	5	.60	.47	0.55			
	13	6	.60	.48	0.56			
	15	7	.55	.65	0.46			
	10	8	.55	.50	0.47			
	17	9	.54	.54	0.51			
	16	10	.54	.40	0.49			
Factor 2 (Knowledge of COVID)	2	11	.84	.75	0.66	2.19	20.62	
	3	12	.79	.66	0.55			
	1	13	.73	.59	0.51			
Factor 3 (Effort to obtain information)	5	14	.83	.71	0.43	1.68	16.20	
	20	15	.73	.68	0.52			

* Communalities

Cronbach's alpha, McDonald's omega (Ω), construct reliability (CR), and average variance extracted (AVE) coefficients of the sub-dimensions of the scale are given in Table 2. Assessing the Cronbach's Alpha, McDonald's omega (Ω), Construct Reliability (CR) and Average Variance Extracted (AVE), also indicated that the scale had good convergent and divergent validity.

Table 2. Convergent and divergent validity, internal consistency, and construct reliability of the COVİD-19 Awareness Scale

Factors	Cronbach's alpha (CI: 95.0%)	Ω	CR	AVE
Protection	0.82	0.82	0.85	0.36
Knowledge of COVID	0.74	0.75	0.83	0.62
Effort to Obtain Information	0.61	0.65	0.76	0.61

Ω: McDonald's omega, CR: Construct Reliability; AVE: Average Variance Extracted.

As a result of the EFA, we concluded that the awareness of people about COVID-19 could be measured with a total of 15 items in 3 sub-dimensions. CFA was conducted to test the validity of the sub-dimensions that resulted from the EFA. The goodness of fit indices obtained as a result of the CFA and the values that these indices should take are given in Table 3. The goodness of fit indices obtained in the first model were slightly below the recommended values, and covariances were detected between some error values. In line with the recommendations of the CFA, covariances between the errors were defined in the first model, thus the modified model was obtained. In case the CMIN/DF value of the modified model was <3 (X^2=157,16, p<.001), the CFI, GFI, NFI, IFI, and TLI coefficients were >0.90, and the AGFI index was between 0.85 and 0.90, the final model was considered to have acceptable compatibility. **Fig. 2** shows the final model of the scale.

Table 3. The fit model indices of CFA of the COVID-19 Pandemic Awareness Scale

Model Fit Indices	Recommended Criteria	First model	Modified model
X^2		213.37	157.16
DF		87	84
P Values	<.005	<.001	<.001
CMIN/DF	<3	2.45	1.87
CFI	≥0.90	0.87	0.92
AGFI	≥0.80	0.86	0.90
GFI	≥0.90	0.90	0.93
NFI	≥0.90	0.85	0.90
IFI	≥0.90	0.87	0.92
TLI	≥0.90	0.83	0.90
RMSEA	<0.08	0.08	0.06

X^2: Chi-Square Value, DF: the number of degrees of freedom for testing the model, CMIN: Chi-square Minimum, CFI: Comparative Fit Index, AGFI: Adjusted Goodness of Fit Index, GFI: Goodness of Fit Index, NFI: Normed Fit Index, IFI: Incremental Fit Index, TLI: The Tucker-Lewis coefficient, RMSEA: Root Mean Square Error of Approximation

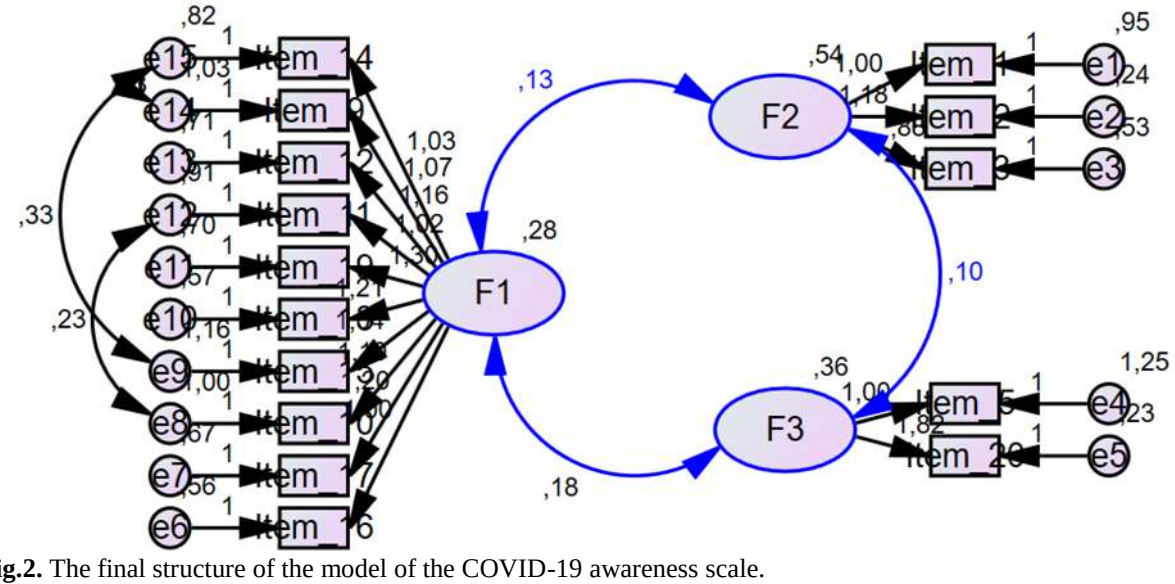

Fig.2. The final structure of the model of the COVID-19 awareness scale.

The increase in the scale scores of the participants indicates that their awareness of COVID-19 has increased. The average score of the participants for the whole scale was 3.92∓0.24. The Knowledge of COVID sub-dimension had the highest mean score (4.09∓0.46). final form of the 15-item COVID-19 awareness scale, created because of this study, is given in the appendix at the end of the study.

DISCUSSION

It has been observed that there are very important scale development studies to reveal

whether there is the necessary awareness in the society about the Covid-19 pandemic (11,12, 13, 14, 15). After the research and analyses conducted in the study titled "Covid-19 Awareness Scale (Covfö) Development Study", it was stated that the 21-item measurement tool COVFÖ, which consists of "Mask, Distance, Hygiene" dimensions, is a valid and safe measurement tool (11).

In the study titled "Turkish Validity and Reliability Study of Knowledge, Attitude,and Behavior Scale Towards COVID-19", it was stated that the 16-item scale consisting of "Clinical Presentations, Routes of Transmission, Prevention and Control, Attitudes, Behaviour" dimensions was reliable and valid after the analyses (12). In the study titled "Multi-Dimensional COVID-19 Scale Development, Validity and Reliability Study"; as a result of the statistical analyses, it was stated that a 22-item scale consisting of three factors as "feelings and behaviours related to COVID-19, thoughts related to COVID-19, and measures taken related to COVID-19" was valid and reliable (13). In the study titled "Scale Development Study Attitude Covid-19 Pandemic", it was stated that the 19item, 5 (five) Likert-type scale consisting of three factors as "Covid-19 Pandemic Precaution, Covid-19 Pandemic Awareness, Covid-19 Pandemic Immunity" was valid and reliable (14). "Development of Coronavirus (Covid-19) Awareness Scale: Validity and Reliability Study", it was stated that the 17-item, 5 (five) Likert-type scale consisting of three factors as "Awareness of Contagion Precautions, Awareness of Following Current Developments, Awareness of Hygiene Precautions" was valid and reliable (15).

It can be stated that the sub-dimensions (factors) obtained in the scales and the statements in the item pools in the scale development studies conducted above in order to reveal whether the necessary awareness has been formed in the society regarding the Covid-19 pandemic overlap with the subdimensions and statements in the item pool obtained in this study. In this study, as in the scale development studies mentioned above, it was preferred to apply a 5 (five) Likert scale (16). In addition, care was taken to ensure that the items of the developed scale were simple and understandable (17).

In this study, we aimed to develop a valid and reliable test in order to evaluate people's awareness of COVID-19. After ensuring the content validity, language, and expression compatibility of the items, they were filled in by 244 participants. After factor loadings, conceptual integrity, and items that could be evaluated under two factors were removed, the 15-item scale form was finalized. The resulting 15-item scale form had three factors and the items under these factors were conceptually compatible with each other. The values obtained as a result of the explanatory factor analysis were at the desired level. The factors obtained as a result of the EFA were named "Protection", "Knowledge of COVID", and "Effort to Obtain Information" respectively.

A confirmatory factor analysis (CFA) was conducted to determine whether the three factors and the 15-item scale resulting from the explanatory factor analysis formed a compatible model. The fit indices obtained from the CFA were within the recommended ranges.

CONCLUSIONS

After analyzing the results of both Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA), we have determined that the COVID-19 Awareness Scale (CAS) is a reliable and valid instrument for assessing people's awareness levels. The COVID-19 awareness scale we have devised can be employed by researchers who seek to measure individuals' awareness levels regarding a pandemic similar to COVID-19. The outcomes of this study will lay the groundwork for researchers intending to develop similar scales in their respective studies.

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Appendix

	Items	**Scoring** I strongly disagree (1), I disagree (2), I have no opinion (3) I agree (4), I strongly agree (5)
1	I do not go to home visits due to the risk of transmission during the covid-19 process.	Protection
2	In the process of Covid 19, shopping malls, markets, etc., where the disease has the highest risk of transmission. I try not to go to mass shopping centers.	Protection
3	In the process of Covid-19, in mass shopping environments, elevators, stairs, streets, parks, etc. I wear my mask in common living areas.	Protection
4	Due to the risk of contamination during the Covid 19 process, I make my payments with tools such as contactless credit card and internet banking.	Protection
5	During the covid-19 process, I keep my meetings in social life as short as possible due to the risk of contamination.	Protection
6	I disinfect my hands to protect myself from Covid-19.	Protection
7	During the covid-19 process, I take care not to use public transport if possible.	Protection
8	I buy the products I need from the internet during the Covid 19 process.	Protection
9	Due to the risk of contamination during the Covid-19 process, I carry out my official transactions over the internet.	Protection
10	I wash my hands periodically to protect myself from Covid-19 disease.	Protection
11	There are vaccines developed by foreign countries that are being applied to protect against Covid-19.	Disease information
12	Covid-19 vaccines are made in 2 and 3 doses.	Disease information
13	Covid-19 is an infectious disease that can cause death.	Disease information
14	I follow the number of Covid-19 patients and cases daily.	Getting information
15	I follow information and current developments about Covid-19 on the official websites of health institutions.	Getting information

RESEARCH ARTICLE

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The Effect of Customized 3D Printed Insoles on Physical Activity Level, Balance, and Physical Performance in Patients with Pes Planus: A Randomized, Placebo Controlled, Double-Blinded Study

ABSTRACT

Objective: This study aimed to investigate the effects of individually designed insoles on physical activity level, balance, and functional performance in patients with pes planus.

Materials and Methods: 38 participants were divided into 2 groups as 3D printed (n=20) and placebo (n=18). In the 3D printed group, medial longitudinal arch support, medial wedge of the foot, medial heel wedge, and transverse arch support were given to the insoles according to the needs of the participants. The placebo group received placebo insoles. Muscle strength, range of motion, static and dynamic balance, physical and physical activity levels were measured at baseline, and eight weeks later (clinicaltrials.gov ID: NCT05306886).

Results: Muscle strengths of the plantar flexion (p=0.030) and eversion increased after the use of insoles in the 3D printed and placebo groups (p=0.020). There was no change in static balance in both groups (p=0.386), but there were significant improvements in dynamic balance in 3D printed groups (p=0.019). Gait speed improved in both 3D printed (p=0.001) and placebo groups (p=0.015). There was no significant difference in the explosive power between the groups (p=0.272). The shuttle run test improved significantly in the placebo group (p=0.015), but no significant change was observed in the 3D printed group (p=0.886). While the physical activity levels in the placebo group showed a significant improvement (p=0.017), the physical activity level decreased in the 3D printed group (p=0.489).

Conclusions: In this study, it was found that the use of personalized insoles is effective in improving physical activity, balance, and performance, while placebo insoles were found to be more effective in increasing muscle strength and explosive muscle strength.

Keywords: Balance, Physical Functional Performance, Pes Planus.

Pes Planuslu Hastalarda Kişiye Özel Tasarlamış 3D Baskılı Tabanlıkların Fiziksel Aktivite Düzeyi, Denge ve Fiziksel Performans Üzerine Etkisi: Randomize, Plasebo Kontrollü, Çift-Kör Bir Çalışma

ÖZET

Amaç: Bu çalışmanın amacı, pes planuslu hastalarda fiziksel aktivite seviyesi, denge ve fonksiyonel performans üzerine kişiye özel olarak tasarlanmış tabanlıkların etkilerini incelemektir.

Gereç ve Yöntem: 38 katılımcı 3D baskılı (n=20) ve plasebo (n=18) olmak üzere 2 gruba ayrıldı. 3D baskılı grupta, katılımcıların ihtiyacına göre tabanlıklara medial longitudinal ark desteği, ayak medial kaması, topuk medial kaması ve enine ark desteği verildi. Plasebo grubu ise plasebo tabanlık aldı. Kas gücü, hareket açıklığı, statik ve dinamik denge, fiziksel ve fiziksel aktivite seviyeleri başlangıçta ve sekiz hafta sonra ölçüldü (clinicaltrials. gov ID: NCT05306886).

Bulgular: Plantar fleksiyon ve eversiyon kas kuvvetleri, 3D baskı ve plasebo gruplarında artış gösterdi (sırasıyla p=0.030 ve p=0.020). Her iki grupta da statik denge değişmedi (p=0.386), ancak 3D baskı gruplarında dinamik denge önemli ölçüde arttı (p=0.019). Yürüme hızı hem 3D baskı (p=0.001) hem de plasebo gruplarında (p=0.015) arttı. Gruplar arasında patlayıcı güçte anlamlı farklılık görülmedi (p=0.272). Shuttle Run testi, plasebo grubunda anlamlı olarak gelişti (p=0.015), ancak 3D baskı grubunda anlamlı değişim gözlemlenmedi (p=0.886). Plasebo grubunda fiziksel aktivite seviyelerinde önemli bir gelişme görülürken (p=0.017), 3D baskı grubunda fiziksel aktivite seviyesi azaldı (p=0.489).

Sonuç: Bu çalışmada, kişiselleştirilmiş tabanlıkların kullanımının fiziksel aktivite, denge ve performansı iyileştirmede etkili olduğu, plasebo tabanlıkların ise kas gücü ve patlayıcı kas gücünü artırdığı bulunmuştur.

Anahtar Kelimeler: Denge, Fiziksel Performans Seviyesi, Pes Planus.

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INTRODUCTION

The foot is an important organ in the human body and acts as a shock absorber for the ground reaction forces exerted on the body (1). It accomplishes this task through the healthy coordination of its joints, ligaments, and muscles. However, disruptions in this healthy coordination can lead to deformities (2). One such deformity, pes planus, is characterized by a low medial longitudinal arch, often accompanied by pronation of the subtalar joint (3). Predisposing factors for pes planus may include degeneration of the plantar fascia, decreased flexibility of the spring ligament, and dysfunction of the tibialis posterior tendon (4, 5).

Pes planus is a foot deformity and can cause pain, instability, and increased risk of injury. Treatment options for patients with this condition include conservative methods such as plaster applications, activity modification, weight loss, shoe modification, taping, foot-ankle orthoses, and custom-made insoles (6, 7). In patients with pes planus deformity, the load on the medial part of the foot increases, and this leads to excessive valgus deformity in the hindfoot (8). The midfoot slides in the transverse tarsal joint with the emergence of the talus head (9). The traction angle of the Achilles tendon shifts laterally to the subtalar joint, promoting eversion. Additionally, Achilles contracture may exacerbate these deformities, potentially resulting in equinus deformity (10).

It is thought that the insoles used in the treatment of pes planus may provide healthy foot mechanics by supporting the foot, allowing painless performance of daily activities and sportive activities, and may also help to reduce the risk of injury (11). Therefore, various types of insoles are used in the treatment of pes planus as a part of conservative treatment (12). However, it is not known which type of insoles is the most effective (13). Recent studies have shown that customized 3D insoles can positively affect gait function and biomechanics (7, 14). However, the number of blinded studies with placebo insoles is limited and more research is needed on the efficacy of custom-made insoles in the treatment of pes planus.

Although the impact of insole usage in individuals with pes planus has been frequently examined in the literature, studies investigating the effectiveness of personalized insoles in treating this condition are relatively scarce. Similarly, there is a limited number of studies in the literature wherein participants were blinded with placebo insoles lacking any support. This study aimed to examine the effects of 3D printed insoles tailored to each patient on physical activity levels, balance, and functional performance in individuals with pes planus.

MATERIAL AND METHODS

A prospective, randomized, controlled, double-blinded design was carried out in this study. Forty-five patients who signed the written informed consent and fulfilled the inclusion criteria were included in the study. Participants aged 18-45 years with pes planus who applied to the Fizyotermal Inc. clinic were included in this study. Permission was obtained from Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (2021245-369) for this study. This study was registered to the NIH Clinical Trials registry, clinicaltrials.gov ID: NCT05306886.

Inclusion criteria were; having a minimum subtalar pronation angle of 5 degrees during standing posture, having a minimum score of + 6 on the Foot Posture Index (FPI) scale, not having received any treatment from the foot area in the last 6 months, having bilateral pes planus. Exclusion criteria were; a history of lower extremity surgery, being an active athlete, pregnancy or diagnosis of malignancy, having a dysfunction such as severe neurological involvement, immobility, cooperation problems that restrict physical activity, having more than 1 centimeter (cm) of lower limb inequality, having a different orthopedic disease that may affect lower limb biomechanics, receiving a different treatment for pes planus at the same with study.

Demographic information, foot posture index, subtalar angles, and leg length were collected in the initial evaluations of the participants. After these data were obtained, dynamic gait analyses and static analyses were taken in a pedobarographic gait analysis device. The footwear habits of each participant were questioned to determine the type of shoes in which the insoles would be used. The patients were divided into two groups by simple computer-assisted randomization as 3D printed and placebo insole groups. Participants were randomly divided into 2 groups without being told which group they were allocated and outcome measurements performed by a physiotherapist who was not aware of group allocation.

Sample size calculation was made with G*Power (Universität Düsseldorf, Kiel, Germany). The sample size was calculated for foot posture index according to Buldt et.al's study (d=0.83) and to achieve $\alpha<0.05$ and $1-\beta=80\%$, 19 patients were required for each group (15).

Outcome Assessments: After collecting demographic information, the participants were called again and normal joint movements, muscle strength, balance evaluations, functional performance tests, and IPAQ questionnaire were performed to determine the level of physical activity. Muscle strength, balance assessments, and functional performance tests were conducted at baseline and eight weeks after the initial assessment.

Foot Posture Index: This test was administered to the participants once during their first visit to evaluate their foot posture. Participants with a test result of +6 points and above were included in the study (16, 17).

Subtalar Angle: Subtalar angle, the range of motion (ROM) of the subtalar joint can be measured with a goniometer to determine whether the hindfoot is in rotation. The severity of subtalar pronation was determined by the goniometric measurement of the subtalar joint (18).

Range of Joint Motion: Ankle inversion/eversion angles were measured with a goniometer to measure the ankle range of motion of the participants. The results were measured three times and mean scores were recorded in degrees.

Muscle Strength Measurement: Muscle strength tests were performed on foot dorsiflexion + inversion, and foot eversion movements to see whether there was a change in muscle strength with insoles. A hand dynamometer was used for the measurements (JTech Commander Power Track II Manual Muscle Testing Dynamometer, USA). Measurements were performed three times for each movement and the highest value was recorded in pounds.

Flamingo Balance Test (FBT): To measure the static balance of the participants, the Flamingo balance test was performed with eyes closed/eyes open. Each participant was asked to place the ankle of the non-tested side behind the knee of the leg on the tested side and stand on one leg for 1 minute. During this time, the number of body oscillations was recorded. Since there were participants who could not complete the one minute, the time spent standing on one leg during the test was also measured and recorded with a stopwatch.

Y-Balance Test (YBT): The previously proven Y-Balance Test Lower Quart (YBT-LQ) was used to measure the dynamic balance of the participants. Participants were asked to stand on one foot on a platform at the center point where all directions intersected while pushing a wooden block on each bar with the other foot. Three measurements were taken in each direction. Three measurements were taken in each direction. The farthest distance was recorded in centimeters. Composite score was calculated as reach distance (cm)/leg length of stance leg (cm) x 100.

Standing Long Jump Test(SLJ): To evaluate the explosive power of the participants, the standing long jump test, the reliability of which has been previously proven and correlated with the vertical jump test, was used (19). During this test, the participants were asked to jump the longest distance they could jump with both feet from the starting line without their feet touching. Each participant performed 3 repetitions. Measurements were made with the help of a tape measure. The highest value was recorded in centimeters.

10-Meter Walk Test (10MWT): To see how the insoles affected the short-term walking speed of the participants, a 10-meter walking test was performed. Participants were asked to walk a previously marked distance of 10 meters at their normal walking speed. The results were measured with a stopwatch and recorded in seconds.

Shuttle Running Test (SRT): A shuttle running test was applied to evaluate the agility of the participants. 2 lines were drawn 7 meters apart. The participant was asked to run as fast as possible behind the start line with the start command. When the participant reached the finish line, he/she turned back to the start line and the time he/she reached the start line for the second time was measured with a stopwatch and recorded in seconds.

Heel Raise Test (HRT): The heel raise test was used to test the ability of the tibialis posterior muscle to maintain inversion in the hindfoot while the forefoot was stabilized on the ground. In this test, which has proven to be reliable, the participants were asked to lift their heels off the floor by rising on tiptoe until fatigue while the forefoot was in inversion on one leg and with the knee in extension. The cadence of the heel-raise cycle was regulated to 60 per minute using a metronome. Participants were directed to raise the heel as high as possible during each heel rise until they could no longer perform additional repetitions while maintaining straightness in the knee and trunk. The number of repetitions was recorded (20).

International Physical Activity Questionnaire (IPAQ): The IPAQ Short Form was used to measure the physical activity levels of the participants and to measure whether they changed with insoles. In this 7-question questionnaire, the Turkish validity and reliability study of which was conducted by Öztürk (2005), the different levels of physical activity levels of individuals in the last week were calculated and recorded in METs (21).

Foot Analysis and Insole Application: All participants walked on a pedobarographic gait analyzer (Postural Electronic Baropodometric Multi-Sensor, Italy), and foot pressure measurements were taken. Among the 3 successful steps, the right and left steps most appropriate for normal gait were selected and recorded. On the same platform, static analyses were taken by asking the participants to stand still while looking straight ahead. Within the scope of the data obtained from the gait analyzer, insoles were drawn with the Milletrix Applicazione MFC program in a computer environment as medial longitudinal arch support, forefoot medial wedge, medial heel wedge, and transverse arch support if necessary. All drawings were made by the researcher's physiotherapist. While drawing the insoles of the intervention group, the MLA height was determined according to the navicular height of each participant while standing. The forefoot medial wedge, medial heel wedge, and transverse arch reinforcement given for each insole were determined according to each participant's analysis. Forefoot medial wedge 3-6 mm, medial heel wedge 1-3 mm, and transverse arch reinforcement 6-8 mm were given and modeled. The total average height of the

insoles in the 3D printed group was calculated as 18.9 mm. The placebo group was modeled with only 2 mm MLA support in the same drawing program. The total height of the insoles in the placebo group was 8.5 mm. Since there is no prescription determined in the literature on the insole design process, all insole design processes and production stages were carried out by the researcher physiotherapist to prevent differences that may arise from the evaluators in this study. The production of the insoles, the design of the insoles through computer software, and the production of the resulting model with a 3D printer eliminated the changes belonging to the practitioner and ensured that the application was made with more precise measurements (24). After the design process was completed, the insoles were transferred to the model processing machine Computer Numerical Control (CNC) machine (CNC router, Italy), and the insoles were produced. To prevent the effects caused by the hardness of the insoles, ethyl vinyl acetate (EVA) of medium hardness (shore 50), whose effectiveness has been previously proven, was used. Standardization was ensured between the insoles through the design process, the production phase, and the materials used, and it was aimed to exclude the differences that would arise at these stages. The produced insoles were corrected with a milling machine to adapt to the participant's shoes. For the upper coating of the finished insoles, 1mm thick fabric was used (Figure 1).

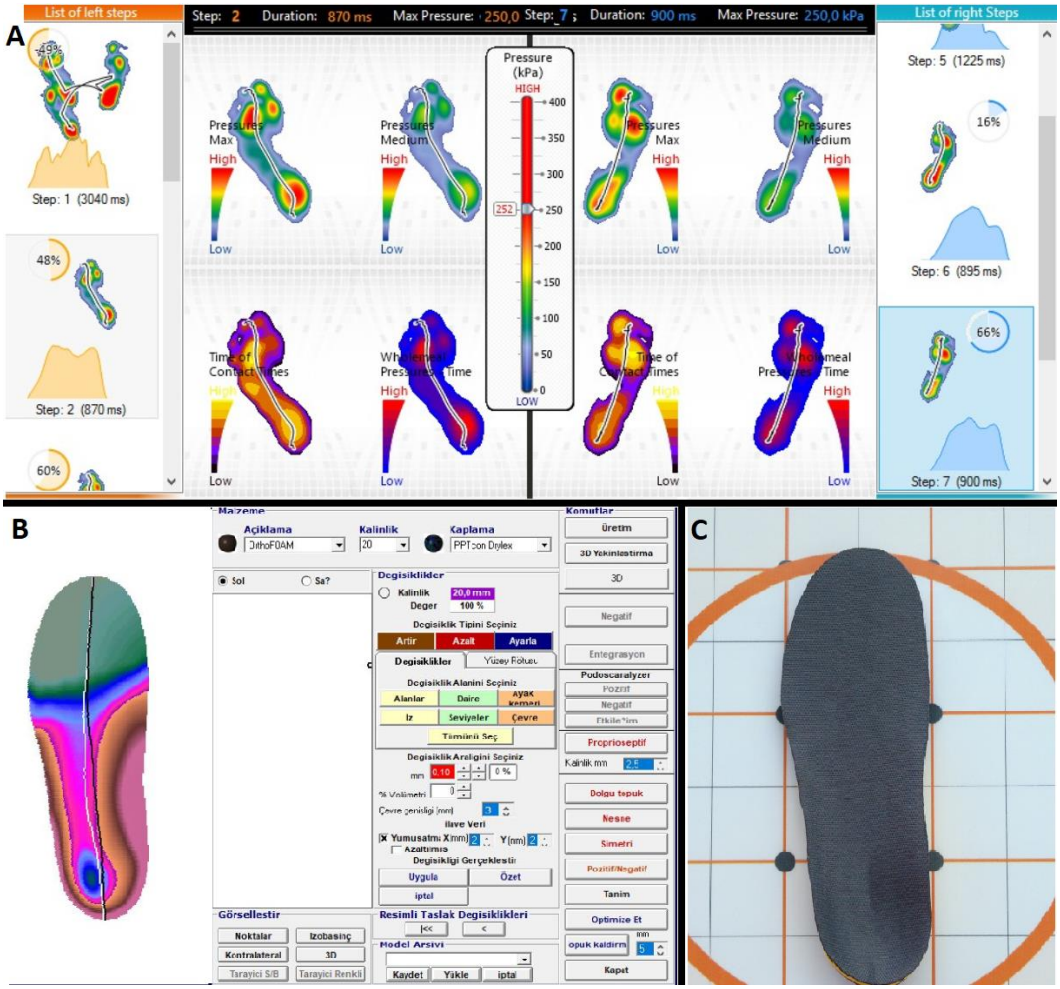

Figure 1. Foot analysis and 3D printed insole**.** A: Pedobarographic analysis, B: Computerized insoles design according to the analysis results, C: Personilized 3D printed insole

Statistical Analysis: Mean and standard deviation were used for descriptive statistics. Shapiro-Wilk test was applied for normal distribution of the obtained data. All evaluation results obtained were analyzed using appropriate statistical methods. Paired-Samples t-Test was applied for comparisons within both 3D printed and placebo groups. An Independent-Sample t Test was applied for comparison between groups. The chi-square test was applied for gender distributions. The statistical significance threshold for all tests was set at $p < 0.05$. Statistical analysis of the data was carried out using SPSS 22.0 for Windows.

RESULTS

A total of 45 participants were included between December 2021 and July 2022, 38 of whom completed this study (Figure 2). Participants' gender, age, body mass index, foot posture index, and

subtalar angles were evaluated (Table 1). In the 3D print group, there were 10 (50%) males and 10 (50%) females, while in the placebo group, 13 (72.2%) were males and 5 (27.8%) were females. There was no significant difference between the sex distribution of the groups (p=0.585). Additionally, there were no significant differences between the age, body mass index, and subtalar angle of the participants at baseline (respectively p=0.839, p=0.556, p=0.109). However, there was a significant difference between the groups in foot posture index scores (p<0.05). The normal distribution of the data of the groups among all outcome assessments was analyzed using the Shapiro-Wilk test, and it was found that all parameters showed a normal distribution (p>0.05).

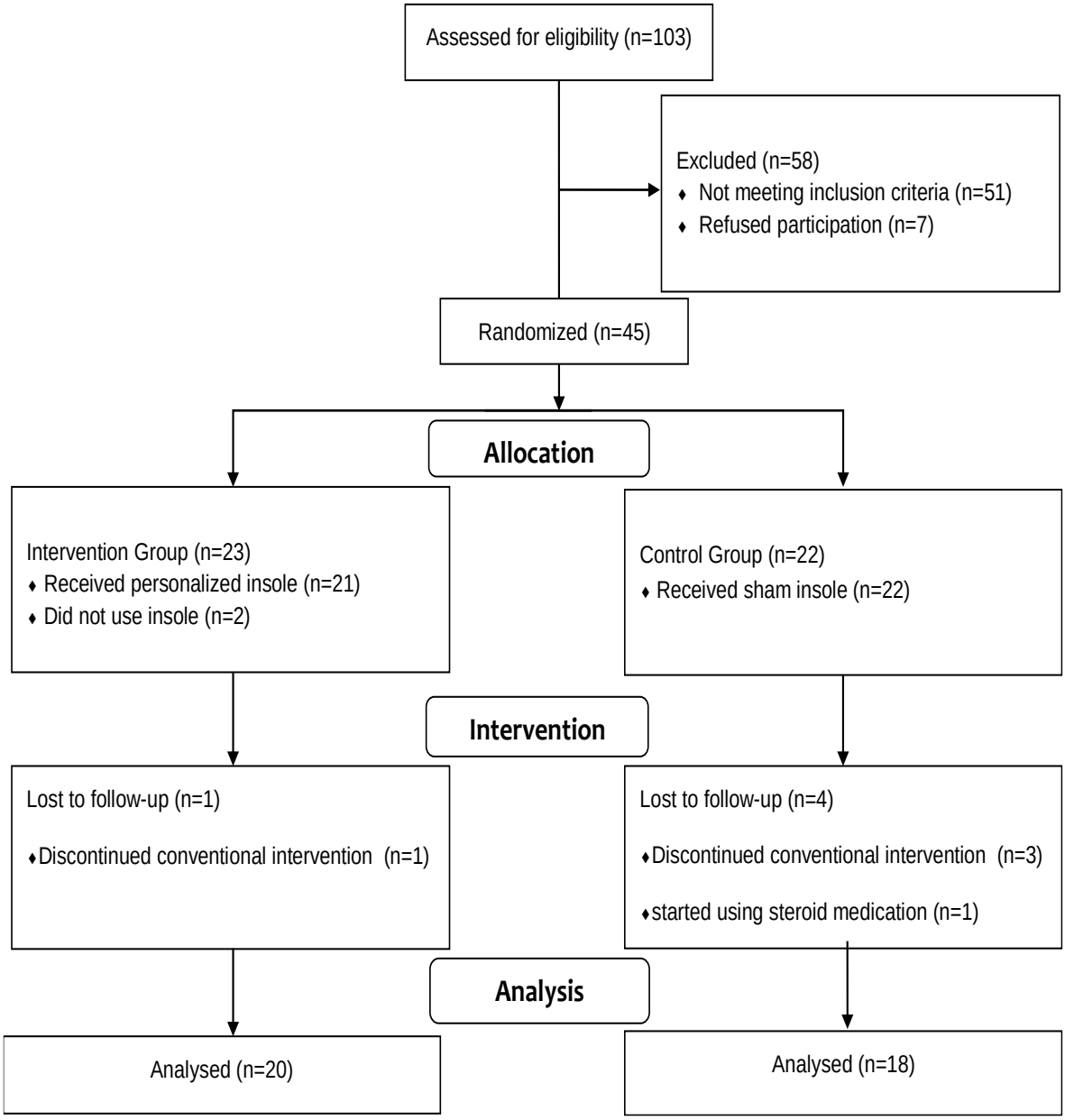

Figure 2. Flowchart

Table 1. The descriptive and statistical results of age and symptom onset of participants

	3D printed Group (n=20)	Placebo Group (n=18)		
	X±SD	X±SD	t	P*
Age (year)	24.01±4.24	23.66±5.74	0.205	0.839
BMI(Kg/cm^2)	23.55±4.68	22.76±3.31	0.595	0.556
Foot posture index	10.35±1.30	9.11±1.49	2.709	**0.010**
Subtalar angle	10.4±1.95	9.22±2.47	-1.643	0.109

BMI: Body mass index, *: independent samples t test, p<0.05

In this study, the FPI score values of the groups were calculated using Cohen's d formula, revealing an effect size of 0.88, with the study's power determined to be 86% through post-hoc power analysis.

Significant differences were observed in the 3D-printed group in plantar flexion and dorsiflexion muscle strength, as well as in the YBT and the 10 MWT, with corresponding p-values of 0.024, 0.030, 0.019, and 0.001, respectively. While the placebo group exhibited significant changes in ROM and SRT, HRT, and IPAQ scores, with respective p-values of 0.026, 0.015, 0.012, and 0.017. Furthermore, both groups demonstrated significant differences in eversion muscle strength between pre- and post-test results (p=0.020, p=0.028). No significant differences were found in the remaining outcome measures (p>0.05) (Table 2).

Table 2. Results of the pre- and post-tests comparison for both groups

	3D printed Group (n=20)			**Placebo Group (n=18)**		
	Pre-test	Post-test	**p**	Pre-test	Post-test	**p**
Eversion ROM	29.05±6.58	28.62±4.76	0.706	29.55±4.44	31.91±3.82	**0.026**
Inversion ROM	37.01±5.61	37.25±10.8	0.855	41.55±10.32	40.72±8.7	0.818
Muscle strength DF (lbs.)	28.5±4.17	30.47±4.84	**0.024**	29.77±4.75	31.61±5.08	0.116
Muscle strength PF (lbs.)	28.6±4.38	31.02±3.10	**0.030**	30.44±3.75	31.36±3.29	0.273
Muscle strength EV (lbs.)	24.95±5.93	27.55±4.26	**0.020**	25.47±3.38	28.41±5.09	**0.028**
Flamingo balance test	12.13±2.42	13.61±1.81	0.386	11.87±1.74	12.40±1.62	0.479
Y balance test total (cm)	217.80±6.15	240.38±4.62	**0.019**	239.47±5.82	241.11±5.97	0.241
Standing long jump (cm)	130.9±31.12	126.8±33.79	0.145	132.05±30.61	131.6±32.09	0.830
10-meter walk (sec)	8.01±0.88	7.26±0.86	**0.001**	7.09±0.75	6.91±0.88	0.181
Shuttle running test (sec)	12.42±1.68	12.47±137	0.886	12.49±1.37	12.06±1.39	**0.015**
Heel raise test (rep.)	35.5±15.86	38.75±16.23	0.072	39.05±21.37	47.16±29.52	**0.012**
IPAQ (METs)	2785.3±2419.4	2450.7±1811.3	0.489	2150.3±2036.8	3010.1±2449.6	**0.017**

ROM: Range of motion, DF: dorsiflexion, PF: plantar flexion, EV: eversion, cm: centimeters, sec: seconds, MET: Metabolic equivalent of task, IPAQ: International Physical Activity Questionnaire, Paired sample t-test, p<0.05

When comparing the mean differences in pre- and post-test results between the groups, a significant difference was observed in the eversion ROM (p=0.038), inversion ROM (p=0.931), YBT (p<0.001), and SRT (p=0.045) scores, favoring the 3D-printed group. Conversely, IPAQ scores showed a significant difference in favor of the placebo group (p=0.046). No significant differences were found in the other outcome measures (p>0.05) (see Table 3).

Table 3. Comparison of 3d printed and placebo groups' pre-posttest differences

	3D printed Group (n=20)	**Placebo Group (n=18)**		
	X±SD	**X±SD**	**t**	**p**
Eversion ROM	0.43±4.07	4.76±7.49	0.876	**0.038**
Inversion ROM	-0.24±7.59	0.83±9.63	0.087	0.931
Muscle strength DF (lbs.)	1.97±3.58	1.83±4.96	0.105	0.917
Muscle strength PF (lbs.)	2.42±4.61	0.91±3.43	1.133	0.265
Muscle strength EV (lbs.)	2.60±4.56	2.94±5.19	-0.217	0.826
Flaming balance test	1.48±2.17	0.53±1.68	-1.496	0.143
Y balance test total	22.58±5.17	1.16±5.88	-11.951	**<0.001**
Standing long jump (cm)	4.05±11.91	0.38±7.57	-1.116	0.272
10-meter walk (sec)	0.74±0.82	0.53±0.61	-0.898	0.375
Shuttle running test (sec)	0.047±0.73	0.42±0.66	2.075	**0.045**
Heel raise test (rep.)	3.25±7.62	8.11±12.1	-1.490	0.145
IPAQ (METs)	334.6±2123.1	859.66±1382.8	-2.029	**0.046**

ROM: Range of motion, DF: dorsiflexion, PF: plantarflexion, EV: eversion, cm: centimeters, sec: seconds, MET: Metabolic equivalent of task, IPAQ: International Physical Activity Questionnaire, Independent sample t-test, p<0.05

DISCUSSION

In this study, which examined the effects of customized 3D printed insoles on physical activity level, balance, and functional performance in patients with pes planus, significant differences were observed in muscle strength, static and dynamic balance, and 10 MWT in the 3D printed group. In the placebo group, significant differences were observed in the normal range of motion of eversion movement, peroneal muscle strength, SRT, HRT, and physical activity levels. While the Y balance test demonstrated a significant increase in the insoles group, there was no difference between the two groups in the FBT results.

In the tests performed to evaluate the foot posture of the participants in this study, significant

differences were found between the 3D printed and placebo groups in the FPI scores. It was thought that this situation might have caused the results of the study. The significant improvements in favor of the placebo group may be due to better foot posture scores. Altered foot alignment could have contributed to lower test scores in this study.

When the literature was reviewed, it was noted that studies on pes planus often included patients with both unilateral and bilateral conditions in the same study. To prevent potential discrepancies stemming from participant variation, only individuals with bilateral pes planus who met the inclusion criteria were enrolled., thus eliminating the effect of asymmetric effect on physical activity and quality of life evaluations.

While Araujo et al. stated that foot orthoses may decrease eversion by increasing afferent feedback (22), Wahmkow et al. found that this was not true in their study (23). In this study, the use of insoles for 8 weeks did not restrict eversion movement and did not increase inversion movement. The placebo group exhibited an increase in eversion movement, which is unfavorable for patients with pes planus. It was concluded that placebo insoles are not beneficial and may potentially be detrimental to patients with pes planus. The absence of medial wedge support in patients with pes planus may have led to an excessive load on the medial aspect of the foot, thereby increasing eversion. This observation suggests that pes planus could be a progressive postural disorder.

Zhao et al. conducted a study measuring ankle muscle strength in 67 men aged 40 to 64 years using an isokinetic device. They discovered a negative correlation between medial arch height and ankle muscle strength, suggesting that the adaptation of the medial arch for weight support and shock absorption influences ankle muscle strength (24). Some studies suggest that orthosis use has neuromuscular effects, and Nigg et al. developed a sensorimotor theory that orthoses may alter afferent stimuli to muscle and proprioceptive sensory endings (25). Jung et al. conducted an 8-week follow-up study involving 28 pes planus patients divided into two groups. One group received customized foot insoles, while the other received customized foot insoles along with short foot exercises. The study revealed an increase in the cross-sectional area of the abductor hallucis muscle and flexor hallucis muscle strength in both groups. However, a more substantial increase was observed in the group that incorporated exercises. (26) . Baur et al. randomly divided 99 runners aged between 18 and 60 years with overuse injuries into intervention and control groups and found that foot orthosis increased activation of the peroneal muscles before heel contact. This suggests that altered afferent input from the foot and other proprioceptive structures may contribute to ankle stability (27). However, some studies show that orthoses do not affect muscle strength (28). According to the muscle strength results of this study, a significant increase in plantar flexion and eversion forces was observed in both groups as a result of analyzing the effects of insoles. It is thought that this increase is caused by the change in afferent input and therefore has a positive effect on muscle contraction. The lack of difference between the groups supports this view. When the long-term effects of the insoles were analyzed, it was observed that the effect of increased afferent input in plantar flexion continued in the intervention group but not in the placebo group. The use of insoles may have corrected the traction angle of the Achilles tendon by positioning the foot more accurately. The reason for the increase in eversion muscle strength in the placebo group may be that the increased eversion angle requires more muscle strength to provide stability in the distal group muscles of the foot. Increased muscle strength in the inversion and eversion directions may be a compensatory effect to stabilize the foot and ankle. Increased muscle strength as a result of the use of insoles may have helped the muscle to be in the optimal position and to realize its potential.

Kuyung and Seop investigated the effect of insoles on balance performance in people with pes planus. In the study, 14 university students were randomly divided into two groups: an insoles-supported group and a short-foot exercise group. Their balance was measured with YBT and it was reported that dynamic balance increased significantly in both groups (29). They stated that the reason for the improvement in the insoles group was the decrease in maximum ground reactions and the emergence of dynamic and biomechanical effects. In this study, static balances did not improve with the use of insoles, but significantly decreased in the placebo group.

In dynamic balance assessments, significant post-test improvements were observed in both the 3D printed and placebo groups following insole use. This enhancement could be attributed to increased activity levels and alterations in ground reaction forces. However, the absence of noticeable effects of insoles in static balance tests might be attributed to proper foot alignment and inadequate stiffness of the insoles.

In a study conducted by Tudor et al. arc index and explosive power of 218 children aged between 11 and 15 years were evaluated. Kistler Quattro jumping force platform was used and it was reported that there was no relationship between arch height and explosive power (30). In this study, no significant change was observed in explosive power nor the post-test scores. This may be due to the fact that jumping involves complex movements that are not only related to plantar flexion muscle strength. Therefore, according to the results of the study, it is thought that explosive strength cannot be related to muscle strength alone and more factors should be

considered to make a significant difference in jump performance.

In a study conducted on healthy young adults, Okunuki et al. examined the effect of increased pronation in the hindfoot on physical performance. In that study, performance tests such as the shuttle running test were used and it was observed that the results of the shuttle running test deteriorated with an increasing degree of pronation in the hindfoot (31). Other studies have also indicated that foot orthoses and shock-absorbing insoles may affect running ergonomics and the mass of the insoles should also be considered (32-34). Researchers have reported that insoles may not have an immediate effect on running performance, but 8 weeks of use may affect performance (34). In this study, it was observed that the insoles in the placebo group outperformed those in the 3D printed group. Possible reasons for this disparity may include initial discomfort and an adaptation process associated with the insoles' use. Consequently, the utilization of insoles might have altered habitual foot positioning and the distribution of tasks among lower extremity muscles, potentially leading to new foot positioning and discrepancies in workload distribution among lower extremity muscles.

The study investigated the impact of shoe usage on the heel elevation test and revealed no significant difference between the test results conducted with or without shoes (35). In our study, we observed an increase in the number of repetitions during the HRT as a result of insole usage, although no significant difference was found between the groups. However, after 8 weeks, a significant increase in repetitions was noted in the placebo group, whereas no such difference was observed in the 3D printed group. We hypothesized that the immediate effect of the insoles was manifested through enhanced plantar flexion muscle strength. Additionally, the participants in the 3D printed group may not have exhibited improvements in test results due to arch supports causing discomfort. Furthermore, the extent of insole usage over the 8 weeks was not documented, raising the possibility that the insoles may not have been sufficiently effective in improving the muscle endurance of the participants.

Lopez-Lopez et al. conducted a study investigating the relationship between arch height and quality of life and reported that there was no significant difference between arch height and physical activity (36). Wrobel et al. conducted a study in which they reported that customized insoles improved physical activity levels compared to prefabricated and placebo insoles (37). However, in this study, it was thought that the insoles might have caused foot discomfort among participants in the 3D printed group, potentially leading to reduced participation in physical activity. This suggests that discomfort in patients with pes planus may increase the possibility of rejection and disuse of insoles. It is thought that the increase in the level of physical activity in the placebo group may also be due to the psychological effects of insoles and that people may have participated in more activities by feeling safer with insoles.

LIMITATIONS

All of the participants used insoles with the shoes they most frequently wore. In this study, participants participated in different types of footwear such as shoes, trainers, and boots. It was thought that participation in future studies with a single type of shoe would yield more accurate results. The inability to categorize participants based on the severity of pes planus may have influenced the study outcomes. Comparing patients with similar degrees of pes planus could potentially yield more robust results. Additionally, the fatigue levels of study participants were not assessed before evaluation, and fatigue levels may impact physical activity scores.

CONCLUSION

The utilization of customized 3D insoles in patients with pes planus led to enhancements in muscle strength, dynamic balance, and muscle endurance of the tibialis posterior muscle, and affected the level of physical activity. The improvements observed in the 3D printed group are believed to stem from increased sensory input from the sole and proper foot biomechanics. Conversely, enhancements in the placebo group are attributed to psychological effects and increased levels of physical activity.

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RESEARCH ARTICLE

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Adults' Awareness about Mask Use

ABSTRACT

Objective: Respiratory pandemics cannot be prevented from spreading if the mask is not worn correctly. This study aims to determine adult's awareness of mask use and the factors that influence mask use.

Materials and Methods: This descriptive study was conducted in a university hospital during the COVID-19 pandemic (June 2020). Participants were asked to complete a questionnaire on socio-demographic characteristics and mask use.

Results: In the presented study, 705 people were included. The mean age of the participants was 35.86±8.77 (18-65) years old and 71.2% (n=502) were male, and 45.5% (n=321) were university graduates. Complete compliance with the pandemic rules was achieved by 83.7% of women (n=170) and 58.0% of men (n=291) (p<0.001). While 77.6% (n=547) used surgical/medical masks, 60.4% (n=426) reported using the same mask more than once. Of these, 44.8% (n=191) washed the mask, 36.9% (n=157) ventilated the mask and 18.3% (n=78) did nothing before reuse. Among mask wearers, 51.9% (n=366) reported breathing difficulties and 33.2% (n=234) reported that wearing a mask had a negative psychological impact.

Conclusions: It has been determined that there is a lack of information on the use of masks, even during the COVID-19 pandemic where the use of masks is mandatory. It is important that the mask is used correctly to provide effective protection. Efforts should be accelerated to ensure that all segments of the society are sufficiently aware of this issue.

Keywords: Masks, COVID-19, Pandemics, Behavior, Public Health.

Yetişkinlerin Maske Kullanımına İlişkin Farkındalığı

ÖZET

Amaç: Solunum yolu ile yayılan salgınların önlenmesi için maskenin doğru şekilde takılması gerekir. Bu çalışmanın amacı, yetişkinlerin maskeye ilişkin farkındalığını ve maske kullanımını etkileyen faktörleri belirlemektir.

Gereç ve Yöntem: Bu tanımlayıcı çalışma, COVID-19 pandemisi sırasında (Haziran 2020) bir üniversite hastanesinde gerçekleştirilmiştir. Katılımcılar sosyo-demografik özelliklerin ve maske kullanımına ilişkin ifadelerin yer aldığı bir anketi cevaplamıştır.

Bulgular: Sunulan çalışmaya 705 kişi katıldı. Katılımcıların yaş ortalaması 35,86±8,77 yıl (18-65) olup, %71,2'si (n=502) erkek, %45,5'i (n=321) üniversite mezunu idi. Kadınların %83,7'si (n=170) ve erkeklerin %58,0'ı (n=291) pandemi kurallarına tam uyum sağladığını belirtti (p<0,001). Katılımcıların %77,6'sı (n=547) cerrahi/tıbbi maske kullanırken, %60,4'ü (n=426) aynı maskeyi birden fazla kez kullandığını bildirdi. Bunların %44,8'i (n=191) maskeyi yıkıyor, %36,9'u (n=157) maskeyi havalandırıyor ve %18,3'ü (n=78) herhangi bir işlem yapmadan yeniden kullanıyordu. Maske kullananların %51,9'u (n=366) solunum güçlüğü yaşadığını ve %33,2'si (n=234) maske takmanın psikolojisini olumsuz etkilediğini belirtti.

Sonuç: Maske kullanımının zorunlu olduğu COVID-19 pandemisi sırasında bile maske kullanımına ilişkin bilgi eksikliği olduğu tespit edilmiştir. Etkili koruma sağlamak için maskenin doğru kullanılması önemlidir. Toplumun tüm kesimlerinin doğru maske kullanmasını sağlamak için çalışmalar hızlandırılmalıdır.

Anahtar Kelimeler: Maskeler, COVID-19, Pandemi, Davranış, Halk Sağlığı.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has impacted the daily lives of people all over the world. After the COVID-19 epidemic was declared in January 2020, various measures were implemented to reduce the spread of the virus, and governments even imposed many sanctions. As of September 2020, wearing a mask has become mandatory in all indoor and outdoor areas except residences in Turkey (1). The obligation to wear a mask outdoors was abolished in March 2022 and began to be implemented in closed environments according to ventilation and distance rules (2). Although the use of masks has become mandatory in epidemics, it may not prevent the spread of the epidemic unless people wear the mask correctly.

Taking into account the current global spread of COVID-19, the measures taken by the World Health Organization (WHO) have been updated and continue to recommend that the public use masks in certain situations. Masks are recommended when a person has or is suspected to have COVID-19 and for people who are in crowded, closed or poorly ventilated areas. It was also announced that recommendations for mask use may change, taking into account local epidemiological trends or increasing levels of hospitalization, vaccination coverage and immunity levels in the community, and the environment in which people find themselves (3). Of course, masks may become necessary again if other viruses spread. Therefore, mask use is an ongoing, important health behavior problem (4).

Medical masks are used to prevent the passage of respiratory secretions excreted by the wearer. It is the type of mask that should be used under normal conditions. Medical masks are disposable and need to be changed as soon as they become moist. Properly worn medical masks are sufficiently protective against aerosols and large droplet splash with more than 95% bacterial filtration efficiency. FFP2 (N95) masks are designed to reduce the wearers' exposure to airborne pollutants, including viruses and bacteria. Vented masks have a valve system that closes while breathing and opens while exhaling. It does not prevent infected people from transmitting the virus to someone else (5).

In a pandemic caused by respiratory diseases, the use of masks affects not only individual health but also the public health of a country. Mask usage habits vary according to cultures. For example; It was determined that Koreans are more accustomed to using masks than other countries (6), and the rate of wearing masks in China is higher than in Poland (7). The use of masks was not common in Turkey before the pandemic. Therefore, research on this topic is limited. The aim of this study is to determine people's awareness of mask use and the factors affecting mask use in a period when masks are mandatory in the COVID-19 pandemic.

MATERIAL AND METHODS

This descriptive study was conducted at Necmettin Erbakan University Medical Faculty Hospital. The ethics committee of Necmettin Erbakan University approved the study. During June 2020, every person, except staff and healthcare professionals, passing through the checkpoint between 10.00-11.00 and 14.00-15.00 on weekdays was informed about the study, and a survey was administered to people over 18 years of age and literate who agreed to participate in the study. The study was conducted during the COVID-19 pandemic when everyone entering the hospital was obliged to wear a mask as part of the pandemic measures.

The first part of the questionnaire included questions on the socio-demographic characteristics of the participants and assessment of self-compliance with the measures taken against the COVID-19 outbreak, the frequency of hand washing, the type of mask used, how they obtained the mask and whether they reused the masks. In the second part, there are 15 statements about how they feel when wearing a mask, why a mask should be worn, issues to consider when using masks, and difficulties encountered with masks. These statements were given the options 'agree', 'undecided' and 'disagree'. Those who gave incomplete answers to the survey questions were excluded from the study.

The data obtained were evaluated using the Statistical Package for Social Sciences for Windows 21.0 (SPSS Inc., Chicago, Illinois, USA) statistical program. Initially, the data were analyzed with descriptive statistics. Categorical data were reported as frequencies while numerical data were expressed by means and standard deviations. For the analytical statistics, Chi-square test for the categorical data. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In the study, 705 people were included. The mean age of the participants was 35.86±8.77 years (min=18; max=65) and 71.2% (n=502) were male, and 45.5% (n=321) were university graduates. Among men, 38.3% (n=270) had a beard and 4.5% (n=32) had shaved their beard due to mask use. Of the participants, 46.8% (n=330) were smokers and 7.1% (n=50) were trying to quit smoking due to the pandemic. The comparison of the socio-demographic characteristics by gender is shown in Table 1.

When the participants were asked most challenging COVID-19 pandemic measures according to them, they reported staying away from relatives and friends (49.7%; n=351), curfew (27.3%; n=192), wearing a mask (19.5%; n=138) and other difficulties (3.5%; n=24), respectively. Of the participants, 77.6% (n=547) used a surgical/medical mask, 57.9% (n=408) purchased the mask, and 60.4% (n=426) used the same mask more than once.

Table 1. Comparison of participants' socio-demographic characteristics by gender

	Total Mean±SD	**Female Mean±SD**	**Male Mean±SD**	**p**
Age	35.86±8.77	35.46±9.3	36.02±8.5	0.443
	n (%)	**n (%)**	**n (%)**	
Education Level				
High school and below	384 (54.5)	93 (45.8)	291 (58.0)	**0.004**
University	321 (45.5)	110 (54.2)	211 (42.0)	
Working status				
Working	554 (78.6)	83 (40.9)	471 (93.8)	**<0.001**
Not working	151 (21.4)	120 (59.1)	31 (6.2)	
Income Level				
Less than expenses	297 (42.1)	94 (46.3)	203 (40.4)	0.216
Equal to expenses	303 (43.0)	85 (41.9)	218 (43.4)	
More than expenses	105 (14.9)	24 (11.8)	81 (16.2)	
Having a chronic disease				
Yes	155 (22.0)	135 (66.5)	415 (82.7)	**<0.001**
No	550 (78.0)	68 (33.5)	87 (17.3)	
Smoking status				
Smoking	380 (53.9)	59 (29.1)	321 (63.9)	
Not smoking	325 (46.1)	144 (70.9)	181 (36.1)	**<0.001**
Total	**705 (100)**	**203 (100)**	**502 (100)**	

Participants who used the mask more than once were asked if they did anything before reusing it. Respectively, 191 people (44.8%) stated that they washed the mask, 157 (36.9%) ventilated it and 78 (18.3%) reused it without any action. Of the female participants, 83.7% (n=70) and 58.0% (n=291) of the males reported complete compliance with the COVID-19 pandemic measures (p<0.001). Table 2 shows the comparison of participants' attitudes towards the COVID-19 pandemic by gender.

Table 2. Comparison of participants' attitudes towards the COVID-19 pandemic by gender

	Total	**Female**	**Male**	**p**
	n(%)	n(%)	n(%)	
Compliance with COVID-19 pandemic measures				
Completely compliant	461(65.4)	170 (83.7)	291(58.0)	**<0.001**
Partially compliant	244(34.6)	33(16.3)	211(42.0)	
Hand washing frequency in the COVID-19 pandemic				
Increased frequency of hand washing	616(87.4)	174(85.7)	442(88.0)	0.398
Unchanged	89 (12.6)	29(14.3)	60(12.0)	
Type of mask used				
Surgical/medical mask	547 (77.6)	160 (78.8)	387 (77.1)	0.619
Non-medical mask	158 (22.4)	43 (21.3)	115 (22.9)	
Mask supplied				
By purchasing	408 (57.9)	136 (67.0)	67 (33.0)	**0.002**
Free of charge	297 (42.1)	272 (54.2)	230 (45.8)	
Frequency of using the same mask				
More than once	426(60.4)	123(60.6)	303(60.4)	0.954
Only one time	279(39.6)	80(28.7)	199(39.4)	
Total	705 (100.0)	203 (100.0)	502 (100.0)	

While 55.7% (n=393) of the participants felt safe when wearing a mask, 25.4% (n=179) believed that the type of mask they wore would protect them from Coronavirus. Wearing a medical mask 25.6% (n=140) and 24.7% (n=39) of those who wore non-medical masks agreed that they believed the mask they wore would protect them from coronavirus (p<0.576). Among mask wearers, 51.9% (n=366) had breathing difficulties and 33.2% (n=234) reported that wearing a mask had a negative psychological impact. Of smokers, 57.4% (n=218) and 73.8% of non-smokers (n=240) agreed that removing and wearing the mask while smoking would increase the risk of contamination (p<0.001). There was a significant association between education levels of those who felt it was unnecessary to wear a mask (p=0.001). Among those with a university degree, 2.5% (n=8) and 7.3% (n=28) of those with a high school degree or less agreed that it was unnecessary to wear a mask. Comparison of the answers of the participants who agreed according to their level of education is shown in Table 3.

Table 3. Comparison of the answers of the participants who agreed according to their level of education

		Education Level		
	Total	**High school and below**	**University**	**p**
	n (%)	**n (%)**	**n (%)**	
I feel safe when I wear a mask	393 (55.7)	213 (55.5)	180 (56.1)	0.872
I have difficulty breathing when I wear a mask	366 (51.9)	192 (50.0)	174 (54.2)	0.266
Wearing a mask protects me from Coronavirus	179 (25.4)	102 (26.6)	77 (24.0)	0.434
Wearing a mask negatively affects my psychology	234 (33.2)	124 (32.3)	110 (34.3)	0.579
If I am a patient/carrier. I should wear a mask to avoid contamination	661 (93.8)	353 (91.9)	308 (96.0)	**0.028**
The mask caused allergies. scars. pimples. etc. on my face	90 (12.8)	47 (12.2)	43 (13.4)	0.647
I think wearing a mask is unnecessary.	36 (5.1)	28 (7.3)	8 (2.5)	**0.004**
I have to wear a mask not to get infected	553 (78.4)	309 (80.5)	244 (76.0)	0.152
In a two-person environment. only one needs to wear a mask.	54 (7.7)	32 (8.3)	22 (6.9)	0.462
I can take off my mask when I talk	56 (7.9)	37 (9.6)	19 (5.9)	0.069
The mask makes me touch my face more often	279 (39.6)	163 (42.4)	116 (36.1)	0.088
The mask is more protective in men without a beard	226 (32.1)	117 (30.5)	109 (34.0)	0.323
The patient/carrier should not wear a mask with a valve	227 (32.2)	135 (35.2)	92 (28.7)	0.066
I can use my mask longer by donning and doffing.	70 (9.9)	43 (11.2)	27 (8.4)	0.218
Taking the mask off and putting it back on while smoking increases the risk of infection	458(65.0)	229 (59.6)	229 (71.3)	**0.001**

DISCUSSION

One of the important changes brought about by the COVID-19 pandemic is the use of masks that have become an inevitable part of our daily lives. Wearing masks has been shown to reduce the risk of healthcare workers becoming infected with COVID-19 by 70% (8). Issues such as the correct use of the mask, what kind of mask should be used, when it should be changed will continue to pose a problem until an adequate level of consciousness is reached in the whole society. It has been shown in many studies that there is a lack of knowledge on this subject, from ordinary citizens to health care professionals (4,6,9). In our study, various information deficiencies were found. The most difficult step in combating the pandemic is to create behavioral change in the society.

The three most important basic principles of protection from COVID-19 are mask, social distance and compliance with hygiene rules (10). In the present study, when respondents were asked about their compliance with the measures announced in the COVID-19 pandemic, nearly two-thirds reported that they completely complied with the rules. It was determined that female participants were more compliant with the pandemic rules compared to male participants. There are studies in the literature that support this result (4,11). In the Woodcock et al. study, the rate of women reporting wearing masks were higher than men (12).

In a study conducted with around 10,000 participants in China during the early stages of the pandemic, when the COVID-19 virus became increasingly widespread, two third of participants reported reusing disposable masks (13). Another study with nursing students and their relatives, one third reported using the same mask more than once (14). In this study, 60% of the participants used the same mask more than once, but when asked about their knowledge of the subject, 90% confirmed that they should not use the mask for long periods of time by putting it on and taking it off. This contradiction is indicating that although the information is known, it is not easy to create positive behavioral change. The reason for the differences in mask use found in the studies may be the prevalence of the virus at the time of the study, and cultural and occupational differences among the participants.

In a study conducted in two North American cities, 14% of the approximately 25,000 mask wearers were found to be wearing their masks incorrectly (15). In the present study, about a quarter of the participants reported using non-surgical masks (home-sewn fabric masks). Of those who used the same mask more than once, about half washed it, one-third ventilated it, and the rest reused it without any action. This high rate of misuse is a major obstacle in the fight against the pandemic. Failure to change the mask often enough may increase the incidence of self-infecting.

Masks were sold at high prices for a while due to insufficient stocks, but the problem was later solved by the government's effective price control and increased production. In order to encourage the use of masks in Turkey, free masks were even distributed by the government (16). However, the insufficient amount of masks in the early periods created a tendency for people to use masks incorrectly. These misuse habits include constant removal and re-use of the mask, washing and re-using, masks made from different fabrics and repeated use. Our research shows that these usage patterns are preferred at certain rates. Some wrong habits are difficult to replace with the correct ones even if a sufficient number of masks are available. Even among highly educated groups, such misuse is common.

One of the challenges of wearing a mask is perceived breathlessness (17). One study conducted at rest or with light to moderate exertion, reported minimal changes in oxygen or carbon dioxide levels while wearing a face mask (18). In the present study, half of the participants reported breathing difficulties when wearing a mask. It should be noted that an individualized approach may be required, particularly for lung patients who may have difficulty tolerating mask wear. The need for hand hygiene in disease prevention is well recognized by most communities (19). In the study by Ugurlu et al. it was found that approximately 90% of the participants had increased hand washing frequency during the pandemic period (20). The rate was similar in the present study. The metanalysis showed that hand hygiene can be beneficial with a relative reduction of 11% in respiratory diseases (21).

The limitation of the study may be that the study population consisted only of people presenting to tertiary healthcare facilities and that it was conducted during a period when mask use was mandatory. However, we believe that our experience of mask use during the pandemic period will be important for comparison with studies to be conducted in other periods.

As a result, it is seen that there is a lack of knowledge on mask use even during the COVID-19 pandemic, when mask use is mandatory. The use of masks was not common in Turkey before the pandemic. Therefore, research on this topic was limited and focused on healthcare workers. This study is important as it is conducted on adults except healthcare workers. For the mask to provide effective protection, it must be used correctly. It is necessary to accelerate interventions in order to reach a sufficient level of awareness in all segments of society.

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RESEARCH ARTICLE

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The Importance of 25 Hydroxyvitamin D Level Monitoring in Children Diagnosed with Juvenile Idiopathic Arthritis

ABSTRACT

Objective: In patients with juvenile idiopathic arthritis (JIA), bone metabolism may be negatively affected due to both the activity of the disease and the medications used. Our study aimed to investigate the necessity of evaluating 25 hydroxyvitamin D (25 (OH) Vit D), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) levels and possible related factors in the follow-up of patients diagnosed with JIA.

Materials and Methods: The records of 68 patients with JIA were retrospectively evaluated. Disease subtypes, medications used, and whether they were in remission or active disease were reviewed.

Results: 25 OH Vit D levels were low in 14.7% of patients with JIA compared to the control group. 66.6% of the patients with systemic arthritis had high ALP levels. 25 OH Vit D level was low in 16.6% of steroid users, and Vitamin D level was low in 55.5% of the patients in the active disease group. It was determined that patients in the active disease group had the highest ALP and lowest vitamin D levels compared to patients in remission with and without medication.

Conclusions: Bone metabolism in patients with JIA is negatively affected. Since vitamin D plays a crucial role in bone metabolism, it was emphasized that vitamin D levels should be evaluated especially during active disease and supplements should be provided for patients with low vitamin D levels.

Keywords: Juvenile Idiopathic Arthritis, Vitamin D, Bone Metabolism.

Juvenil İdiyopatik Artrit Tanılı Çocuklarda 25 Hidroksivitamin D Düzey Takibinin Önemi

ÖZET

Amaç: Juvenil idiyopatik artrit (JİA)'li hastalarda gerek hastalığın aktivitesi gerekse kullanılan ilaçlar nedeni ile kemik metabolizması olumsuz etkilenebilir. Çalışmamızda JİA tanılı hastaların takibinde 25 hidroksivitamin D (25 (OH) Vit D), kalsiyum (Ca), fosfor (P), alkalen fosfataz (ALP) düzeyleri ve ilişkili olabilecek faktörlerin değerlendirilmesinin gerekliliğini araştırmak amaçlandı.

Gereç ve Yöntem: JİA tanılı 68 hastanın kayıtları retrospektif olarak değerlendirildi. Hastalık alt tipleri, remisyon durumu, kullanılan ilaçlar incelendi.

Bulgular: Kontrol grubuna kıyasla JİA hastalarının %14,7'sinde vitamin D düzeyinin düşük olduğu bulundu. Sistemik artriti olan hastaların %66,6'sında ALP düzeyinin yüksek olduğu saptandı. Steroid kullananların %16,6'sında vitamin D düzeyi düşük bulundu. İlaçlı ve ilaçsız remisyondaki hastalarla kontrol grubu arasında biyokimyasal parametreler açısından fark yoktu. Aktif hastalık grubundaki hastaların %55,5'inde vitamin D düzeyleri düşük saptandı. Aktif hastalık grubundaki hastaların, ilaçlı ve ilaçsız remisyondaki hastalar ile karşılaştırıldığında, en yüksek ALP ve en düşük vitamin D düzeyine sahip oldukları saptandı.

Sonuç: JİA'lı hastalarda kemik metabolizması olumsuz etkilenmektedir. D vitamininin kemik metabolizması üzerinde önemli rol oynaması nedeni ile bu hasta grubunda özellikle aktif hastalık sırasında vitamin D düzeylerinin bakılması ve D vitamini düşük saptanan hastalara vitamin D desteği verilmesi gerekliliği vurgulandı.

Anahtar Kelimeler: Juvenil İdiyopatik Artrit, D Vitamini, Kemik Metabolizması.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a systemic disease characterized by chronic idiopathic synovitis and the presence of extra-articular manifestations (1). Although the actual prevalence of JIA remains unclear, the average incidence and prevalence of JIA are 9-25/100000 and 12-113/100000, respectively (2). The prevalence in our country was determined to be 64/100000 in one study (3). Although the disease is generally twice as common in females than males, it is more common in boys in developing countries.

Etiology of JIA is not known with certainty but many genetic, hormonal, environmental, and infectious factors are considered to be involved in its pathogenesis (1, 4). Infiltration of activated lymphocytes and macrophages into the synovium and cytokines released from these cells are thought to play a role in the pathogenesis of JIA (5). Tumor necrosis factor-alpha (TNF-α), a cytokine released from macrophages, has a critical role in developing local inflammation and tissue damage. TNF-α stimulates the production of Interleukin 8 (IL-8), monocyte chemotactic protein (MCP) and collagenase. IL-8 stimulates leukocyte infiltration, and mitogen-activated protein kinase phosphatase (MKP) stimulates macrophage activation. Collagenase is the key enzyme in collagen degradation and destroys the extracellular matrix in the synovium. TNF-α exerts its effect through its two receptors at the cellular level: TNF Receptor 1 (TNFR1) (p55) and TNF Receptor 2 (TNFR2) (p75). Other cytokines responsible for the development of inflammation and tissue damage, although not as much as TNF-α, are IL-1, IL-2, IL-4, IL-6, and transforming growth factor-P (TGF-P) (4, 5).

Although the role of vitamin D in bone metabolism has been well accepted for a long time, studies have also indicated that it has an immune system regulatory effect. Vitamin D inhibits the immune response of Type 1 T helper (Th1) cells and reduces the production of inflammatory cytokines such as IL-17, IL-1, IL-6, and TNF-α. Therefore, the risk of infections and autoimmune diseases increases in vitamin D deficiency (6). Bone metabolism is adversely affected in patients with JIA due to disease activity, duration, medications, restriction of physical activity, and malnutrition. Since vitamin D deficiency is a preventable and treatable condition, the present study investigated the levels of 25(OH) vitamin D, calcium, phosphorus, and alkaline phosphatase in pediatric patients with JIA followed up in our clinic and evaluated possible related factors.

MATERIAL AND METHODS

The records of 68 patients diagnosed with JIA were retrospectively evaluated according to the International League of Associations for Rheumatology (ILAR) criteria in the pediatric rheumatology outpatient clinic between 1995 and 2009. A control group was formed with thirty-nine healthy children. Consent was obtained from the families of both groups. Disease subtypes, medications used, and whether they were in remission or active disease were evaluated. Ca, P, ALP, and 25(OH) vitamin D levels were evaluated in all patients, and these values were compared with those of the control group. The relationship of Ca, P, ALP, 25(OH) vitamin D values with disease subtypes, disease activity, and medications used was investigated, and statistical studies were performed. The normal limits of the laboratory parameters were 8.8-10.6 mg/dl for calcium, 2.5-4.5 mg/dl for phosphorus, 3.5-5.2 g/dl for albumin, 30-120 U/L for alkaline phosphatase and 10-44 ng/ml for 25(OH) vitamin D measured by RIA method. Values outside these reference ranges were considered pathological. Demographic characteristics of the patients (age, gender, height, weight, and body mass index percentiles), JRA subtypes, medications used in the last year, whether osteoporotic doses of steroids were used, last clinical status (remission with or without medication and active disease) and the relationships of the laboratory parameters we examined were statistically evaluated. SPSS (Statistical Package for the Social Sciences) version 13 assessed the study's findings. While evaluating the study data, in addition to descriptive statistical methods (Mean, Standard deviation), the Chi-Square test and Fisher's Exact Chi-Square test were used to compare qualitative data. The statistical significance was evaluated at the $p<0.05$ level.

RESULTS

Of the 68 patients with JIA included in the study, 42 were female, and 26 were male. The mean age was 4.5±2.12 years (3-21). There were 16 females and 23 males in the control group. No difference was determined between the mean ages of both groups ($p>0.005$). Similarly, there was no difference between the two groups regarding height, weight, body mass index, and follow-up periods. The latest status of the patients in terms of disease activities is presented in Table 1.

Table 1. Current status of patients

Final status	Number of patients (n)	Ratio (%)
Active disease	14	20.5
Remission w/medication	27	39.7
Remission w/o medication	27	39.7

w/: with w/o: without

When the calcium, phosphorus, ALP, and 25(OH) Vit D values of the patient group and the control group were compared, it was observed that the 25(OH) Vit D value in the patient group was lower than in the healthy group and the difference was statistically significant ($p=0.013$) (Table 2).

Table 2. Biochemical analysis of patients diagnosed with JIA and the control group

	Ca			P			ALP			25 (OH) Vit D		
	N	H	L	N	H	L	N	H	L	N	H	L
Patients	64	0	4	51	16	1	63	5	0	58	0	10
Control group	36	1	2	35	4	0	36	3	0	39	0	0
p-value	0.41			0.16			1.00			0.013		

Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, 25 (OH) Vit D: 25 Hydroxyvitamin D, N: normal, L: low, H: high

Steroid use above the physiological dose (<5 mg/m²/day prednisolone and equivalent) was considered an osteoporotic dose. When a comparison was made between steroid users and non-users at osteoporotic doses among patients with JIA, it was statistically significant that serum 25 (OH) Vit D levels were lower in the steroid users (p=0.013). There was no statistically significant difference between the serum calcium, phosphorus, ALP, and 25 (OH) Vit D values of patients using steroids and patients using other medications. When patients with active disease were compared with the healthy group, ALP level was statistically significantly higher (p=0.04), and 25(OH) Vit D level was lower, which was statistically significant (p=0.001) (Table 3).

Table 3. Biochemical comparison of patients with active disease and the control group

	Ca			P			ALP			25 (OH) Vit D		
	N	H	L	N	H	L	N	H	L	N	H	L
Active disease group	12	0	2	9	5	0	10	4	0	9	0	5
Control group	36	1	2	35	4		36	3		39	0	0
p-value	0.46			0.04			0.07			0.001		

Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, 25 (OH) Vit D: 25 Hydroxyvitamin D, N: normal, L: low, H: high

There was no difference between the patients in medicated remission and the control group regarding the examined biochemical values. Similarly, no difference was determined between patients in drug-free remission and the control group. There was no statistical difference between patients in medicated remission and those in drug-free remission regarding serum calcium, phosphorus, ALP, and 25(OH) vitamin D levels. Patients with drug-free remission were compared with those having an active disease, and in the active disease group, higher ALP and lower vitamin D levels were statistically significant (p=0.01 and p=0.03, respectively) (Table 4).

Table 4. Biochemical comparison of drug-free remission and active disease group

	Ca			P			ALP			25 (OH) Vit D		
	N	H	L	N	H	L	N	H	L	N	H	L
Active disease group	12	0	2	9	5	0	10	4	0	9	0	5
Remission w/o medication	26	0	1	23	4	0	27	0	0	25	0	2
p-value	0.26			0.231			0.01			0.03		

Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, 25 (OH) Vit D: 25 Hydroxyvitamin D, N: normal, L: low, H: high

DISCUSSION

Juvenile idiopathic arthritis is a disease characterized by idiopathic, chronic synovial inflammation that is common in childhood. According to the ILAR diagnostic criteria, it is divided into seven subtypes (1). In studies conducted in various countries, the mean incidence was reported to be 9.2-25/100,000 and the prevalence 12-113/100,000 (2). A study from our country determined it to be 64/100.000 (6). Although JIA is more common in girls in developed countries, the disease is more common in boys in developing countries. In our study, female patients were predominant in the gender distribution (42 females, 26 males). There are two peak ages at which the disease occurs most frequently, the first being 1 to 3 years of age and the second being nine years, and the mean age of our patient population was approximately four years, consistent with the literature. While the oligoarticular type is the most common subtype of JIA in developed countries, the polyarticular subtype comes to the fore in developing countries. In our study, the oligoarticular type was 41.1%, and the polyarticular type was 8.4%.

In various studies, laboratory investigations of bone mineralization and physiology of children with JIA have revealed different results (7-10). One study demonstrated that patients with systemic JIA had normal calcium, phosphorus, and osteocalcin levels but elevated ALP levels. This condition is explained by the more severe joint destruction and bone destruction in the systemic form (10). In our study, similar to the literature, we determined that the ALP level was high only in the systemic form of the JIA subgroups.

Vitamin D metabolism is often impaired in patients diagnosed with JIA, both due to lack of intake and as side effects of the medications used. According to the study conducted by Bianchi et al.

on 36 patients diagnosed with JIA, some of whom used steroids, the 25 (OH) Vit D levels of children with polyarticular and systemic diseases were lower than the control group. This decrease is considered to be due to a decrease in 1.25(OH) vitamin D production and receptor number (11). In our study, 25(OH) vitamin D levels were statistically significantly lower in patients diagnosed with JIA compared to the control group (p=0.013).

In severe chronic inflammatory diseases such as JIA, osteoblast-osteoclast balance is disrupted due to the increase in IL-1A, IL-6, IL-7, TNF alpha and beta, and osteoporosis may occur. In addition, corticosteroids used in treatment also negatively affect bone metabolism. Steroids increase bone resorption and the effects of parathormone on bone, suppress the synthesis function of osteoblasts, inhibit intestinal calcium absorption, and cause hypercalciuria. In our study, 25(OH) vitamin D levels were found to be statistically significantly lower in patients diagnosed with JIA who used osteoporotic doses of steroids compared to those who did not, which was consistent with the literature.

When children with active disease and patients in remission with and without medication were compared, respectively, it was revealed that 25(OH) vitamin D levels were low in the group with active disease, while ALP values were high. Studies have reported that patients with JIA have bone mineralization disorders even without steroid use (12-14). Our findings are also compatible with the literature as it was thought that the higher bone destruction in active disease and the use of high doses of steroids were effective (15, 16).

Osteopenia was observed in approximately 40% of patients with JIA, and some of these patients developed pathologic bone fractures at a later age (17).

In our study, vitamin D levels were low in some patients diagnosed with JIA. In this disease, in which bone metabolism is adversely affected, we recommend that vitamin D levels should be evaluated and vitamin D support should be provided together with calcium when necessary.

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RESEARCH ARTICLE

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Artificial Intelligence Readiness Status of Medical Faculty Students

ABSTRACT

Objective: This research aims to examine the knowledge level and awareness of Faculty of Medicine students about medical artificial intelligence technologies.

Materials and Methods: In this study involving students studying at Medical Faculties in Turkey, descriptive questionnaire, and the Medical Artificial Intelligence Readiness Scale for Medical Students (MAIRS-MS) were applied.

Results: MAIRS-MS score distributions were lower for students who thought that the use of artificial intelligence in the field of health conflicted with their professional knowledge (p=0.001), future goals (p<0.001), and would create negativities if not used correctly (p=0.006). It was found that the MAIRS-MS score distributions of students who think that artificial intelligence technologies will contribute to the development of the profession (p=0.003), and reduce the workload (p<0.001), who can distinguish under which conditions they will use artificial intelligence or not (p<0.001), and who think that they have enough knowledge to make the necessary explanation to patients who have concerns about artificial intelligence (p<0.001), have higher MAIRS-MS score distributions. When the students' follow-up of current information about artificial intelligence technologies in health was examined, it was found that the ethics and ability sub-dimension score distributions were similar (p=0.771; p=0.069), while the cognition and vision sub-dimension score distributions differed (p<0.001; p=0.014). When the situation of distinguishing under what conditions to use or not to use artificial intelligence was examined, it was found that the ethics sub-dimension score distributions were similar (p=0.088), while the cognition, vision and ability sub-dimension score distributions differed (p<0.001; p=0.003; p=0.001). When the situations of thinking that artificial intelligence training would contribute to the profession were evaluated, it was found that the cognition sub-dimension score means were similar (p=0.340), and when the use of artificial intelligence in the field of health conflicted with professional knowledge, the vision sub-dimension score distributions were found to be similar (p=0.112).

Conclusions: It is seen that the students' awareness level about medical artificial intelligence is high, and they have the ability to use artificial intelligence technologies.

Keywords: Artificial intelligence, Artificial Intelligence Applications in Medicine, Education, MAIRS-MS, Technology.

Tıp Fakültesi Öğrencilerinin Yapay Zekâ Hazırbulunuşluk Durumları

ÖZET

Amaç: Bu araştırmada Tıp Fakültesi öğrencilerinin tıbbi yapay zekâ teknolojileri hakkındaki bilgi düzeyleri ve farkındalıklarının incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Türkiye'deki Tıp Fakültelerinde öğrenim gören öğrencilerin katıldığı bu çalışmada, tanımlayıcı bir anket ve Tıp Fakültesi öğrencileri için Tıbbi Yapay Zekâ Hazır Bulunuşluk ölçeği (Medical Artificial Intelligence Readiness Scale for Medical Students-MAIRS-MS) uygulanmıştır.

Bulgular: Yapay zekanın sağlık alanında kullanılmasının mesleki bilgi (p=0.001), gelecek hedefleri ile çeliştiğini (p<0.001), doğru kullanılmaması halinde olumsuzluklar yaratacağını (p=0.006) düşünen öğrencilerin MAIRS-MS puan dağılımları daha düşük olmasına rağmen yapay zekâ teknolojilerinin mesleğin gelişmesinde katkısı olacağını (p=0.003), iş yükünü azaltacağını (p<0.001) düşünen, yapay zekayı hangi koşullar altında kullanıp kullanmayacağını ayırt edebilen (p<0.001), yapay zekâ konusunda endişeleri olan hastalara gerekli açıklamayı yapabilecek kadar bilgisi olduğunu (p<0.001) düşünen öğrencilerin, MAIRS-MS puan dağılımları daha yüksek olduğu bulunmuştur. Öğrencilerin sağlıkta yapay zekâ teknolojileri ile ilgili güncel bilgileri takip etme durumu incelendiğinde, etik ve beceri alt boyut puan dağılımlarının benzer olduğu (p=0.771; p=0.069), bilişsel ve öngörü alt boyut puan dağılımlarının farklılık gösterdiği bulunmuştur (p<0.001; p=0.014). Yapay zekayı hangi koşullar altında kullanıp kullanmayacağını ayırt etme durumu incelendiğinde, etik alt boyut puan dağılımlarının benzer olduğu (p=0.088), bilişsel, öngörü ve beceri alt boyut puan dağılımlarının farklılık gösterdiği bulunmuştur (p<0.001; p=0.003; p=0.001). Yapay zekâ eğitiminin mesleğe katkı sağlayacağını düşünme durumları değerlendirildiğinde bilişsel alt boyut puan ortalamalarının benzer olduğu (p=0.340), yapay zekanın sağlık alanında kullanılması mesleki bilgi ile çelişme durumu incelendiğinde, öngörü alt boyut puan dağılımlarının benzer olduğu bulunmuştur (p=0.112).

Sonuç: Öğrencilerin tıbbi yapay zekâ konusundaki farkındalık düzeylerinin yüksek olduğu ve yapay zekâ teknolojilerini kullanma becerilerine sahip oldukları görülmüştür.

Anahtar Kelimeler: Yapay Zekâ, Tıpta Yapay Zekâ Uygulamaları, Eğitim, MAIRS-MS, Teknoloji.

INTRODUCTION

Artificial intelligence refers to systems or machines that imitate human intelligence to perform tasks and gradually improve themselves with the information they collect. Even though we are not generally aware of it, it has become an important part of almost all our daily lives. It is also a fact that there are very few people knowledgeable about the applications and concepts behind these technologies. It is anticipated that these technologies can facilitate complex processes and important repetitive tasks, especially in the healthcare industry. In this regard, it has become clear that healthcare professionals and doctors need to be informed and improve themselves on this subject (1). Therefore, it is important to investigate the level of artificial intelligence readiness among medical students (2).

The concept of artificial intelligence was first used in 1965. By modeling human learning, inference, and development, it makes it easier to automatically solve problems that are difficult to solve with simple calculations. It is thought to have its roots in the short story "Runaround", about a robot developed by engineers, published by Isaac Asimov in the 1940s. In the 1950s, Alan Turing developed a code-breaking machine called The Bombe, which is considered the first working electro-mechanical computer, and published an article explaining how to make smart machines and test their intelligence. The Turing Test described in this article is still used to determine the intelligence of an artificial system. Robotics, one of the places where artificial intelligence is used, is a type of artificial intelligence and is the combination of industrialized robots and computers. The robot is taught how the job should be done using artificial intelligence technology (3). Another type used is the simulation of human perception systems and skills such as vision, hearing and touch. These artificial intelligence skills can be achieved to a certain extent in today's technology. One of the artificial intelligence applications used in education is expert systems. Expert systems by definition; They are computer programs that perform the tasks of people who specialize in a certain field using many artificial intelligence algorithms. They work based on inference and knowledge. Expert systems are a branch of artificial intelligence. However, there are also features that distinguish it from artificial intelligence. Artificial intelligence mimics human intelligence when solving a problem; Expert systems, on the other hand, deal with problems that can be solved by experts on certain subjects. Expert systems are also used in distance education and provide individual answers and feedback to students (4).

The first interactions between medicine and artificial intelligence occurred in the 1960s with the creation of the Medical Literature Analysis and Retrieval System (MEDLINE) created by the National Library of Medicine and the web-based search engine PubMed (5). During this process, clinical informatics databases and medical record systems also began to be created for the first time. It was observed that the first studies of artificial intelligence in the field of medicine, which was built based on the "if, then" sequence after Alan Turing's idea of using the computer to simulate intelligent behavior and critical thinking, were on the manual diagnosis of diseases (6). CASNET (Causal Associational Networks), one of the first applications in which artificial intelligence was associated with medicine, is a consultation system created for glaucoma in the 1960s. This model can apply information about specific diseases to individual patients and guide doctors regarding treatment. MYCIN was developed in the early 1970s with the aim of diagnosing certain antimicrobial infections and recommending drug therapy. PIP (Present Illness Program) was developed to simulate the behavior of a nephrologist in taking the current disease history of a patient with underlying kidney disease. In the early 1982s, INTERNIST-1 was developed using a larger database than its predecessors to assist the primary care physician in diagnosis (7). Although all these developments are exciting, these systems have not reached widespread use. The focus has been on machine learning, also known as statistical learning, which is a completely data-driven learning procedure that avoids the hassle of manually coding rules. Machine learning represents a versatile learning framework roughly similar to artificial neural networks (8).

Machine learning analyzing large and complex data sets offers a very promising path to better understanding pathophysiology and, as a result, improving medical search, diagnosis, and treatment for millions of people with chronic and acute diseases (9). The spectrum of AI developments has also been expanded to provide treatment services. The revolution created by the American company Intuitive in the field of surgery, especially urological and gynecological surgeries, with its Da Vinci robotic surgery system can be given as an example (10). With the studies carried out, the areas of use of artificial intelligence in medicine are also expanding considerably. For example, with the digitalization of deep learning and medical image formats, which are sub-branches of artificial intelligence in the field of image processing, artificial intelligence has become extremely important in the field of healthcare. The aim here is to turn a process that can cause great difficulties in terms of cost and time in favor of patients, people and institutions involved in the research task (11). In recent years, there have been many clinical and basic science advances in artificial intelligence in the cardiovascular field, which has significantly reduced the mortality and morbidity rate in hundreds of thousands of patients. Some of these advances; heart failure and transplantation, advanced cardiac

imaging, structural and interventional cardiology, and congenital cardiology (12).

Although medicine has experienced major changes in recent years, medical education is still largely based on traditional curricula and there are no accreditation requirements regarding artificial intelligence in medical education. However, at the 2018 annual meeting of the American Medical Association, it was seen that artificial intelligence encouraged research on how it should be handled in medical education, and it was predicted that this was a harbinger of changes (13). This lack of artificial intelligence integration in medical education poses a challenge to students in the transition from the pre-clinical environment to the clinical environment and how artificial intelligence knowledge can be applied and used in the clinical environment. This brings with it the need to teach machine learning and its applications in medical school and to train the next generation of clinicians and biomedical scientists to face data-driven challenges that may directly affect patient care in the coming years (14).

It is a fact that current medical school students will work with various artificial intelligence technologies when they start their working lives (15). In this case, it is important to examine whether medical school students' opinions about artificial intelligence, their current knowledge about artificial intelligence, and whether they have prejudices about the use of artificial intelligence. In this context, in a study examining medical faculty students' approaches to artificial intelligence, when physician candidates were asked whether they had heard of the concept of artificial intelligence before, it was determined that 93.6% of the students had heard of the concept of artificial intelligence before, and 6.4% had never heard of this concept before. In the same study, when students were asked whether artificial intelligence applications were useful in their medical lives, it was observed that 87% found artificial intelligence applications in health useful (16). This situation shows that most students studying at medical school are aware of artificial intelligence and are positive about using artificial intelligence in their professional lives. However, although it is rare, there is also a group of students who think that with the development of artificial intelligence technology, the physician's margin of error should be small, otherwise they may face pressure (17).

MATERIAL AND METHODS

Ethic Approval: Ethics committee approval for this study, which aims to examine the knowledge level and awareness of Faculty of Medicine students about medical artificial intelligence technologies, was received on 26.04.2022 in Izmir Katip Celebi University Social Research Ethics Committee (2022/08-03). The data collection tools were prepared on Google Forms and the data was obtained between May 2022-February 2023. Participation in the study was completely voluntary. A survey form consisting of socio-demographic questions and the Medical Artificial Intelligence Readiness Scale for Medical Students-MAIRS-MS were administered online to the volunteers participating in the study.

Sample Size: Priori power analysis before the study was performed using the G*Power 3.1.9.4 program. In the comparison of the means of the medical artificial intelligence readiness total score according to more than two group categories (ANOVA: Fixed effects, omnibus one-way), considering the Type I error as 0.05, the minimum effect size as 0.10 and the power of the study as 0.80, 172 participants were included in this study.

Data Collection: The data was gathered using the "descriptive questionnaire" and " Medical Artificial Intelligence Readiness Scale (MAIRS-MS)". Medical Artificial Intelligence Readiness Scale was developed by Ozan Karaca, et al. in 2021. A four-factor structure emerged in the scale: Cognition (items 1-8), Ability (items 9-16), Vision (items 17-19) and Ethics (items 20-22). The validity and reliability of the scale was calculated by Ozan Karaca, et al. and the cronbach alpha reliability coefficient was calculated as 0.870, indicating high reliability (18).

The Medical Artificial Intelligence Readiness Scale for Medical Students (MAIRS-MS) scale reliability of this study was found to be 0.944. The Cronbach alpha value was calculated as 0.901 for cognition score items, 0.915 for ability score items, 0.816 for vision score items, and 0.837 for ethics score items. In our study, as a data collection method, an 18-item descriptive questionnaire, consisting of 3 demographic questions and 15 artificial intelligence questions was applied. It was aimed to determine the awareness of Faculty of Medicine students about the use of medical artificial intelligence with a survey consisting of closed-ended questions. Additionally, the Medical Artificial Intelligence Readiness Scale was administered to the participants. The scale consists of 4 factors (cognition, ability, vision, and ethics) and a total of 22 items, all of which are positive. The representation of the numbers to evaluate these items is determined as strongly agree (5), agree (4), neutral (3), disagree (2), and strongly disagree (1) (19). In line with the participants' answers to the prepared questionnaire form and MAIRS-MS scores, the MAIRS-MS cognition, ability, vision, and ethics sub-dimensions scores were calculated, and the overall total score was obtained. Cognition, ability, vision and ethics subscale scores and MAIRS-MS score were considered as dependent variables. The descriptive questionnaire questions, prepared with closed-ended questions consisting of a total of 18 items, were considered as independent factors. MAIRS-MS score and sub-dimension score distributions were compared according to each category.

Statistical Analysis: The Shapiro-Wilk test was used for normality testing. Descriptive statistics are given as mean and standard deviation

(*Mean*±*SD*) or median (Q_1-Q_3) for continuous variables. Descriptive statistics for categorical variables are reported as frequencies and percentages. Homogeneity of variances was evaluated with the Levene test. In comparing the data of the descriptive questionnaire with the scale sub-dimensions and MAIRS-MS, it was evaluated with the Mann Whitney *U* test, considering the assumptions of normal distribution in case of two independent categories, and the One-way Analysis of Variance (ANOVA) or Kruskal Wallis test more than two independent categories. If there was a statistical difference between groups, Dunn's Bonferroni adjustment results were reported for pairwise comparisons. The relationship between the scale sub-dimensions and the MAIRS-MS scores was evaluated with the Spearman correlation coefficient. The reliability of the scale was determined by the Cronbach alpha value. The value of $p<0.05$ was determined as the level of statistical significance. The data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows, 26.0, IBM corp., Armonk, NY, USA).

RESULTS

A total of 172 students, 83 (48.3%) males and 89 (51.7%) females, took part in this study. The ages of the students range from 18-26, mean and standard deviation 20,86±1,464, median age is 21. Participation was provided from 12 different universities in Turkey, the majority of which were Izmir Katip Çelebi University (58.7%). Participation was provided from every year of the Faculty of Medicine, but it was observed that the participants were mostly students in years 3 (52.9%).

Table-1 shows the rates of response given to the descriptive questionnaire asked to the participants about artificial intelligence in medicine.

Table 1. Descriptive questionnaire regarding artificial intelligence readiness (*n*=172)

Questions	No *n (%)*	Undecided *n (%)*	Yes *n (%)*
***Q*1.** Do you think that artificial intelligence technology will contribute to the development of your profession?	1 (0.6)	38 (22.1)	133 (77.3)
***Q*2.** Do you think artificial intelligence technology will reduce your workload?	7 (4.1)	38 (22.1)	127 (73.8)
***Q*3.** Can you distinguish under what conditions you will or will not use artificial intelligence?	13 (7.6)	81 (47.1)	78 (45.3)
***Q*4.** Do you have enough knowledge to make the necessary explanation to patients who have concerns about artificial intelligence?	49 (28.5)	82 (47.7)	41 (23.8)
***Q*5.** Do you think that training on artificial intelligence will contribute to your profession?	5 (2.9)	45 (26.2)	122 (70.9)
***Q*6.** Does the use of artificial intelligence in the field of health conflict with your professional knowledge?	81 (47.1)	76 (44.2)	15 (8.7)
***Q*7.** Do you think that the use of artificial intelligence in health will reveal new treatments?	14 (8.1)	51 (29.7)	107 (62.2)
***Q*8.** Do you follow current information about artificial intelligence technologies in health?	68 (39.5)	65 (37.8)	39 (22.7)
***Q*9.** Can you foresee and prevent the negative effects that artificial intelligence technologies may cause you?	31 (18.0)	96 (55.8)	45 (26.2)
***Q*10.** Can you use artificial intelligence technologies in front of the patient in a way and method appropriate to the problem?	21 (12.2)	72 (41.9)	79 (45.9)
***Q*11.** Can you use artificial intelligence technologies within ethical principles while doing your job?	10 (5.8)	66 (38.4)	96 (55.8)
***Q*12.** Can you explain how artificial intelligence works and the benefits it brings to you?	25 (14.5)	81 (47.1)	66 (38.4)
***Q*13.** Does the use of artificial intelligence in healthcare conflict with your future goals?	91 (52.9)	66 (38.4)	15 (8.7)
***Q*14.** Do you think that artificial intelligence will create negativities if it is not used appropriately in healthcare?	35 (20.3)	45 (26.2)	92 (53.5)
***Q*15.** Do you think that using artificial intelligence technologies in healthcare will enable us to approach the patient more competently and, when necessary, more knowledgeably, and will help in the continuity of the patient's treatment?	4 (2.3)	51 (29.7)	117 (68.0)

MAIRS-MS score and subdimension mean and standard deviation (min-max) scores found to be that 70,37±16,01 (22-110) for MAIRS-MS; 23,00±6,70 (8-40) for cognition; 27,30±6,85 (8-40) for ability; 9,75±2,59 (3-15) for vision and 10,31±2,8 (3-15) for ethics, respectively. MAIRS-

MS reliability Cronbach alpha value was found to be 0.944, and 0.901, 0.915, 0.816 and 0.837 for the cognition, ability, vision, and ethics sub-dimensions.

The distribution of MAIRS-MS and sub-dimension scores according to response categories for the questions 1-8 is shown in Table 2. Artificial intelligence technology will contribute to the development of profession (p=0.003), reduce the workload (p<0.001), the ability to distinguish under what conditions will use it or not (p<0.001), they have enough knowledge to make the necessary explanation to patients who are concerned about artificial intelligence (p=0.003), the use of artificial intelligence in medicine does not conflict with your professional knowledge (p=0.011), MAIRS-MS scores were found to be higher in students who think that the use of artificial intelligence in health will reveal new treatments (p=0.001) and who follow current information about artificial intelligence technologies in medicine (p=0.006).

Table 2. The distribution of MAIRS-MS and sub-dimension scores according to response categories for question 1-8

		No *Mean*±*SD* or *Median* (Q_1-Q_3)	Undecided *Mean*±*SD* or *Median* (Q_1-Q_3)	Yes *Mean*±*SD* or *Median* (Q_1-Q_3)	*p* value
Q1	Cognition	-	20 (17-24)	24 (19.5-28)	**0.004**$^{+}$
	Ability	-	24 (17-30)	29 (24-33)	**0.002**$^{+}$
	Vision	-	9 (6-11)	10 (9-12)	**0.023**$^{+}$
	Ethics	-	9 (7-12)	11 (9-12)	**0.029**$^{+}$
	MAIRS-MS	-	64.50 (45.75-74.25)	73 (64-81)	**0.003**$^{+}$
Q2	Cognition	18 (13-24) ^{a}	19.5 (17-25) ^{a}	24 (20-28) ^{b}	**0.001**$^{+++}$
	Ability	24 (19-28) $^{a, b}$	23.50 (17.75-27.50) ^{a}	30 (24-33) ^{b}	**<0.001**$^{+++}$
	Vision	9 (8-15) $^{a, b}$	8.5 (6-10.25) ^{a}	10 (9-12) ^{b}	**0.002**$^{+++}$
	Ethics	9 (8-14) $^{a, b}$	9 (7-10.25) ^{a}	11 (9-12) ^{b}	**0.002**$^{+++}$
	MAIRS-MS	66 (50-74) $^{a, b}$	63.5 (47-72) ^{a}	74 (64-83) ^{b}	**<0.001**$^{+++}$
Q3	Cognition	20.16 ± 6.27 ^{a}	22.30± 5.64 ^{a}	*27.78* ± 6.78 ^{b}	**<0.001**$^{++}$
	Ability	26 (21-30.50) ^{a}	27 (23-32) ^{a}	32 (24.5-36) ^{b}	**0.001**$^{+++}$
	Vision	9 (7-11) ^{a}	10 (8-11) ^{a}	11 (9-12.5) ^{b}	**0.003**$^{+++}$
	Ethics	10 (8-12)	10 (9-12)	12 (9-13.5)	0.088^{+++}
	MAIRS-MS	66 (56-77) ^{a}	71 (61-79) ^{a}	81 (68.5-90) ^{b}	**<0.001**$^{+++}$
Q4	Cognition	20.08± 7.89 ^{a}	21.77±5.63 ^{a}	24.77± 7.12 ^{b}	**0.004**$^{++}$
	Ability	23 (17.5-32) ^{a}	25 (21-30) ^{a}	32 (25.75-34) ^{b}	**<0.001**$^{+++}$
	Vision	9 (6.5-12.5) $^{a, b}$	9 (7-11) ^{a}	11 (9-12) ^{b}	**0.003**$^{+++}$
	Ethics	9 (5.5-12)	10 (8.5-12)	12 (9-13)	**0.032**$^{+++}$
	MAIRS-MS	63.08± 21.27 ^{a}	66.07 ± 13.53 ^{a}	76.04 ± 15.74 ^{b}	**<0.001**$^{++}$
Q5	Cognition	21.20±11.520	21.91±5.067	23.48±6.99	0.340^{++}
	Ability	23 (14-23) ^{a}	25 (19-29.5) ^{a}	30 (24-33) ^{b}	**<0.001**$^{+++}$
	Vision	7 (5-10) ^{a}	9 (6-11) ^{a}	10 (9-12) ^{b}	**0.026**$^{+++}$
	Ethics	9 (6-13) $^{a, b}$	9 (7-11) ^{a}	11 (9-13) ^{b}	**0.002**$^{+++}$
	MAIRS-MS	65 (36.5-74.5) $^{a, b}$	66 (54.5-73) ^{a}	74 (63-83) ^{b}	**0.003**$^{+++}$
Q6	Cognition	24.43±7.10 ^{a}	21.25±6.30 ^{b}	24.13±4.14 $^{a, b}$	**0.009**$^{++}$
	Ability	30 (24-33.5) ^{a}	25.5 (20.25-31) ^{b}	26 (24-33) $^{a, b}$	**0.015**$^{+++}$
	Vision	10 (9-12)	9 (7-11)	10 (7-12)	0.112^{+++}
	Ethics	11 (9-13) ^{a}	10 (8-12) $^{a, b}$	9 (8-10) ^{b}	**0.013**$^{+++}$
	MAIRS-MS	76 (65-85) ^{a}	67 (57.25-78) ^{b}	66 (63-80) $^{a, b}$	**0.011**$^{+++}$
Q7	Cognition	20.50 (15-24) ^{a}	22 (18-25) ^{a}	24 (19-29) ^{b}	**<0.001**
	Ability	28.5 (21-33.25) $^{a, b}$	24 (18-28) ^{a}	30 (24-33) ^{b}	**<0.001**$^{+++}$
	Vision	10 (6.75-12) $^{a, b}$	9 (6-10) ^{a}	10 (9-12) ^{b}	**0.008**$^{+++}$
	Ethics	9.5 (7.75-13.25) $^{a, b}$	9 (8-11) ^{a}	11 (9-13) ^{b}	**0.035**$^{+++}$
	MAIRS-MS	65.36±19.54 $^{a, b}$	64.45± 14.10 ^{a}	73.84± 15.52 ^{b}	**0.001**$^{++}$
Q8	Cognition	20.97± 7.46 ^{a}	22.38± 4.32 ^{a}	27.56± 6.54 ^{b}	**<0.001**$^{++}$
	Ability	28 (23-32.75)	26 (23-31)	32 (24-35)	0.069^{+++}
	Vision	10 (7-11) ^{a}	10 (7-11) ^{a}	10 (9-12) ^{b}	**0.014**$^{+++}$
	Ethics	11 (8-12)	11 (9-12)	10 (9-13)	0.771^{+++}
	MAIRS-MS	70 (59.25-79.75) ^{a}	71 (61.5-78) ^{a}	76 (66-88) ^{b}	**0.006**$^{+++}$

$^{+}$Mann Whitney *U* test; $^{++}$ One way Analysis of Variance (ANOVA); $^{+++}$ Kruskal Wallis test

Superscripts *a* and *b* indicate the difference between groups mean or median. Any measurements with shared superscript letters are not significantly different from each other at p<0.05 with Dunn-Bonferroni adjustment.

The distribution of MAIRS-MS and sub-dimension scores according to response categories for the questions 9-15 is shown in Table 3. The students' MAIRS-MS scores were found to be higher who can foresee and prevent the negative effects that artificial intelligence technologies may create (p<0.001), can use artificial intelligence technologies in a way and method appropriate to the problem in front of the patient (p<0.001). Also, it has been observed that students who can use artificial intelligence technologies within the framework of ethical principles (p<0.001), explain how artificial intelligence works and the benefits it provides (p<0.001), use artificial intelligence in health services and do not conflict with their future goals have higher MAIRS-MS scores (p<0.001). MAIRS-MS scores were also high for the students who thought that using artificial intelligence technologies in medicine, which could lead to negativities if not used correctly in medicine (p=0.006), would enable them to approach the patient more competently and, when necessary, more knowledgeably, and would help the continuity of the patient's treatment (p<0.001).

Table 3. The distribution of MAIRS-MS and sub-dimension scores according to response categories for question 9-15

		No *Mean*±*SD* or *Median* (Q_1-Q_3)	Undecided *Mean*±*SD* or *Median* (Q_1-Q_3)	Yes *Mean*±*SD* or *Median* (Q_1-Q_3)	*p* value
***Q*9**	Cognition	19.26±6.55 [a]	22.85±5.81 [b]	25.89±7.32 [c]	**<0.001** [++]
	Ability	24.68± 8.62 [a]	27.15±5.88 [a, b]	29.44±6.90 [b]	**0.010**[++]
	Vision	9 (6-12) [a]	10 (8-11) [a]	11 (9-12) [b]	**0.002**[+++]
	Ethics	9 (6-12) [a]	11 (9-12) [b]	11 (9-13) [b]	**0.021**[+++]
	MAIRS-MS	61.58± 18.57 [a]	70.09±13.33 [b]	77.00±16.68 [c]	**<0.001**[++]
***Q*10**	Cognition	19.43±7.51 [a]	21.60±5.76 [a]	25.23±6.58 [b]	**<0.001** [++]
	Ability	21 (17-24.5) [a]	26 (23-30) [b]	32 (26-34) [c]	**<0.001**[+++]
	Vision	7 (6-10) [a]	9.5 (7-11) [a]	11 (9-12) [b]	**<0.001**[+++]
	Ethics	8 (5.5-9.5) [a]	10 (9-12) [b]	12 (9-13) [b]	**<0.001**[+++]
	MAIRS-MS	55.62± 18.14 [a]	66.96± 12.18[b]	77.39±14.95 [c]	**<0.001**[++]
***Q*11**	Cognition	20.50±4.33 [a, b]	20.36± 6.09 [a]	25.07±6.61 [b]	**<0.001** [++]
	Ability	19 (17.75-27.75) [a]	24 (19-28) [a]	31 (26-34) [b]	**<0.001**[+++]
	Vision	8 (6-12) [a, b]	9 (6-10) [a]	11 (9-12) [b]	**<0.001**[+++]
	Ethics	7.5 (6-12.25) [a]	9 (8-11) [a]	12 (9-13) [b]	**<0.001**[+++]
	MAIRS-MS	59.5 (47-75) [a]	64 (53.75-70.25) [a]	77 (69.6-85) [b]	**<0.001**[+++]
***Q*12**	Cognition	19.20±7.32 [a]	21.94±5.37 [a]	25.74±6.93 [b]	**<0.001** [++]
	Ability	23.04± 7.34 [a]	25.30± 6.21 [a]	31.38±5.22[b]	**<0.001** [++]
	Vision	8 (6-9.5) [a]	9 (7-11) [a]	11 (10-12) [b]	**<0.001**[+++]
	Ethics	8 (5.5-9) [a]	10 (8.5-12) [b]	12 (9.75-13) [c]	**<0.001**[+++]
	MAIRS-MS	58.20± 17.12 [a]	66.48± 13.04 [b]	79.74±13.86 [c]	**<0.001** [++]
***Q*13**	Cognition	23.99±7.16 [a]	21.03±5.65[b]	25.67± 0.14 [b]	**0.006** [++]
	Ability	31 (26-33) [a]	24 (18.75-29) [b]	25 (23-29) [a, b]	**<0.001**[+++]
	Vision	10 (9-12) [a]	9 (6-11) [b]	12 (10-12) [a]	**<0.001**[+++]
	Ethics	11 (9-13) [a]	9 (7.75-12) [b]	9 (8-12) [a, b]	**0.007**[+++]
	MAIRS-MS	77 (67-84) [a]	64 (55-73) [b]	71 (65-74) [a, b]	**<0.001**[+++]
***Q*14**	Cognition	26.20±7.49 [a]	21.84±5.235 [b]	22.35±6.71 [b]	**0.006** [++]
	Ability	27 (23-32) [a, b]	24 (18-29) [a]	30 (24-33) [b]	**0.001**[+++]
	Vision	10 (9-12) [a, b]	9 (7-10.5) [a]	10.5 (9-12) [b]	**0.024**[+++]
	Ethics	10 (9-13) [a, b]	9 (8-11) [a]	11 (9-12) [b]	**0.025**[+++]
	MAIRS-MS	76 (61-85) [a]	66 (55-73) [b]	73.5 (64.25-81.75) [a]	**0.006**[+++]
***Q*15**	Cognition	21.50 (14.25-25) [a, b]	21 (17-24) [a]	24 (19.50-29) [b]	**0.010**[++]
	Ability	24.50 (20.25-34.75) [a, b]	24 (18-27) [a]	31 (25-34) [b]	**<0.001**[+++]
	Vision	7.5 (6-12.75) [a, b]	9 (6-10) [a]	10 (9-12) [b]	**<0.001**[+++]
	Ethics	9.5 (6.75-13.75) [a, b]	9 (7-10) [a]	12 (9-13) [b]	**<0.001**[+++]
	MAIRS-MS	63.5 (52.75-80.25) [a, b]	64 (50-70) [a]	76 (65.5-84.5) [b]	**<0.001**[+++]

[++] One way Analysis of Variance (ANOVA); [+++] Kruskal Wallis test

Superscripts *a*, *b* and *c* indicate the difference between groups mean or median. Any measurements with shared superscript letters are not significantly different from each other at p<0.05 with Dunn-Bonferroni adjustment

The relationship between the sub-dimension of the scale and the MAIRS-MS score was examined with Spearman correlation analysis. There was statistically significant moderately positive relationship between cognition and ability (*rho*=0.535; p<0.001); cognition and vision (*rho*=0.402; p<0.001); cognition and ethics (*rho*=0.402; p<0.001); ability and vision

(*rho*=0.668; *p*<0.001); ability and ethics (*rho*=0.686; *p*<0.001); vision and ethics (*rho*=0.587; *p*<0.001). It was observed that there was a strong positive relationship between ability and MAIRS-MS (*rho*=0.895; *p*<0.001); cognition and MAIRS-MS (*rho*=0.788; *p*<0.001); vision and MAIRS-MS (*rho*=0.720; *p*<0.001); ethics and MAIRS-MS (*rho*=0.730; *p*<0.001).

DISCUSSION

This study aims to evaluate the medical artificial intelligence (AI) readiness levels of students at Medical Faculties in Turkey. Their readiness was measured through the total marks that the students scored on the medical AI readiness scale, which included four factors: cognition, ability, vision, and ethics. A higher score indicated a higher agreement with the questionnaire statements, and a higher level of readiness towards AI among medical students in Turkey.

Most students in this study had a mean score on the MAIRS-MS. This result is supported by a previous a cross-sectional study in Malaysia and cohort study in the United Kingdom. Results of the study conducted with 105 participants in Malaysia showed that the mean score of readiness for artificial intelligence was 75.04. The mean scores of cognition, ability, vision, and ethics factors were found as respectively 27.61; 27.17; 10.19 and 10.07. From these mean scores, the total score of the majority of medical school students (67.62%) is 53-83 points, followed by 24.76% of the students with a total score of 84-114 points and 7.62% of the students with a total score of 84-114 points. It was determined that students who score a total of 22-52 on MAIRS-MS. This showed that most of the students had average scores on MAIRS-MS (20). Almost half of a total of 484 medical students at UK medical schools stated that they had a clear understanding of the basic computational principles that underpin artificial intelligence (21).

According to our findings, participants think that medical artificial intelligence has positive results in the field of medicine, but they do not feel fully ready for it. Most of our participants studying at Medical Faculties in Turkey think that artificial intelligence will contribute to their profession and education and reduce their workload. Most people have concluded that the use of artificial intelligence technologies in healthcare will enable us to approach the patient more competently and, when necessary, more knowledgeably, and will also help in the continuity of the patient's treatment (22).

Due to the impact of artificial intelligence on medicine and medical education, many studies have evaluated medical students' views on artificial intelligence, aiming to bring further improvements to this method (23). Abid et al. investigated Pakistani medical students' attitudes and readiness towards AI (24). On the other hand, there are significant issues regarding knowledge, attitude, and preparedness regarding artificial intelligence in some developing countries. Hamd et al. the study results showed a lack of education and training programs for the implementation of AI, and from their perspective, organizations were not well prepared and had to ensure their AI readiness (25). In the United Arab Emirates, Boillat et al. They reported unfamiliarity with AI and called for specific training in medical schools and hospitals to enable them to use this new paradigm to improve healthcare delivery and clinical outcomes (26). The differences between developed and developing countries appear to be largely driven by curriculum designs, particularly the role or lack thereof of artificial intelligence. For this reason, it is recommended that medical faculties consider information sharing mechanisms about artificial intelligence and develop curricula that will teach the use of artificial intelligence tools as a competence (27).

It is of great importance to use artificial intelligence in harmony with the values of society and to protect human rights. Privacy and security of personal data is a fundamental ethical issue that must be considered in the use of artificial intelligence systems. In the questions asked under the ethics sub-dimension, the majority said that they could act in accordance with ethical principles when using artificial intelligence in medicine.

This original research has some minor limitations. We collected data from 6 different public medical schools, mostly from the Aegean and Mediterranean geographical regions, and therefore the findings may not be generalizable to most public and private medical schools. Additionally, the study was conducted only in Turkey. Therefore, although the probability of this difference is very small, the results may not be generalizable to other countries. The findings presented in this study need to be examined carefully considering differences between countries and cultures.

CONCLUSION

Artificial intelligence refers to systems or machines that mimic human intelligence to perform tasks and gradually improve themselves with the information they collect. With this technology, which we use everywhere in our lives and almost all day, especially in medical education and the health sector, information and complex processes and repetitive important tasks can be facilitated. Therefore, it is important to investigate the level of artificial intelligence readiness among medical students. When the findings are evaluated, it is seen that the students' awareness level about medical artificial intelligence is high, and they have the skills to use artificial intelligence technologies. However, it was observed that their self-confidence in technical matters was not very high. The idea has arisen that education on these issues should be emphasized and the self-confidence of medical students should be increased in artificial intelligence skills.

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RESEARCH ARTICLE

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Investigation of the Relationship Between Cervical Disc Herniations and Shoulder Complex Pathologies

ABSTRACT

Objective: The aim of our study was to investigate whether there is a relationship between shoulder complex pathologies and cervical disc herniations.

Materials and Methods: This study retrospectively included 524 patients with both dominant extremity shoulder and neck magnetic resonance examinations obtained from the information processing unit of Duzce University Faculty of Medicine between 01.08.2009-01.08.2023. The results were compared in Statistical Package for Social Sciences (SPSS).

Results: A total of 524 patients, 153 (29.2%) males and 371 (70.8%) females, with a mean age of 51.17±13.70 (range, 13-93) years, were included in the study. According to the statistical analysis of our study, 410 of the participants had supraspinatus pathology, 234 had infraspinatus pathology, 243 had subscapularis pathology and 11 had teres minor pathology. In addition, a statistically significant relationship was found between other shoulder pathologies and herniations at the C4-C5 and C5-C6 disc level ($p<0.05$).

Conclusions: In conclusion, even if there is a significant relationship between cervical disc herniations and shoulder pathologies, different methods should be developed for treatment algorithms and pain management. Evaluation of the cervical region should not be neglected in patient groups with shoulder pathologies.

Keywords: Supraspinatus, Disc Herniations, Shoulder Complex, Neck Pain.

Servikal Disk Herniasyonları ile Omuz Kompleks Kuşağı Patolojileri Arasında Ki İlişkinin İncelenmesi

ÖZET

Amaç: Çalışmamızın amacı, omuz kompleks kuşağı patolojileri ile servikal disk herniasyonları arasında bir ilişki olup olmadığını araştırmaktır.

Gereç ve Yöntem: Bu çalışma retrospektif olarak 01.08.2009-01.08.2023 tarihleri arasında X Üniversitesi Tıp Fakültesi bilgi işlem biriminden alınan hem dominant ekstremite omuz hem de boyun manyetik rezonans incelemesi bulunan 524 hasta dahil edilmiştir. Sonuçlar Statistical Package for Social Sciences (SPSS) te karşılaştırıldı.

Bulgular: Çalışmaya yaş ortalaması 51.17±13.70 (dağılım, 13-93) yıl olan 153 (%29.2) erkek ve 371 (%70.8) kadın olmak üzere toplam 524 hasta dahil edildi. Çalışmamızın istatistiksel analizine göre, katılımcıların 410'unda supraspinatus patolojisi, 234'ünde infraspinatus patolojisi, 243'ünde subskapularis patolojisi ve 11'inde teres minör patolojisi vardı. Ayrıca, diğer omuz patolojileri ile C4-C5 ve C5-C6 disk seviyesindeki herniasyonlar arasında istatistiksel olarak anlamlı bir ilişki bulunmuştur ($p<0,05$).

Sonuç: Sonuç olarak, servikal disk herniasyonları ile omuz patolojileri arasında anlamlı bir ilişki olsa dahi tedavi algoritmaları ve ağrı yönetimi konusunda daha farklı yöntemler geliştirilmelidir. Omuz patolojileri olan hasta gruplarında servikal bölge değerlendirilmesi ihmal edilmemelidir.

Anahtar Kelimeler: Supraspinatus, Disk Herniasyonları, Omuz Kompleks Kuşağı, Servikal Ağrı.

INTRODUCTION

Neck pain is one of the oldest and most common problems that people face. Works related to this subject were found on papyrus in Egypt 4600 years ago. Hippocrates has various studies related with cervical injuries and cervical traction applications (1). Today, it takes its place after low back pain in the ranking of chronic pain. One out of every three people in the general population complains of neck pain that develops due to various causes at some time in their lives (2). The probability of radicular and spinal cord symptoms in people with neck pain remains below 3% (3). Shoulder pain is the third most common musculoskeletal system pathology (4). In recent years, the term shoulder complex has been used instead of shoulder pain because of difficulties in the management of shoulder pain and because of the complex anatomy of that region. In current treatment approaches, there are studies suggesting that the cause of pain is not always related to an injury and this has led to the development of different treatment strategies in clinics (bio-psycho-social treatment models)(5). The primary pathology of pain in the shoulder region may not always be rotator cuff lesions. In a study examining the causes of shoulder pain, pain radiating from the cervical region was found to be 5% (6). The innervation of the rotator cuff muscles, which have important functions in shoulder functions, is realised by the nerves formed by the C4 and C6 nerve roots. It has been emphasised that especially C5 radiculopathy mimics rotator cuff lesions, pain is usually localised in the shoulder, and there may be weakness in shoulder abduction and external rotation (7). Although there is no randomised or cohort study on this subject in the literature, the muscles in the shoulder girdle may be affected in cases where the cervical nerve roots are compressed. Therefore, conditions affecting the functionality of the neck, shoulder and upper extremity may occur.

The neck contains many structures sensitive to pain. Epidural venous structures, duramater, periosteum, vertebral bodies, nerve roots, dorsal root ganglion, muscular structures, facet joints, ligaments and intervertebral discs are pain sensitive structures (8, 9). The intervertebral disc is a non-sensitive structure and does not contain nucleus pulposus nerve tissue or nerve termination (55). Magnetic resonance imaging (MRI) classifications of disc herniations are still currently defined as 4 different stages (Bulging, Protruding, Sequestrated, Extruded) (10).

Rotator cuff muscles consist of supraspinatus, infraspinatus, subscapularis and teres minor muscles.

M.supraspinatus originates from the supraspinal aponeurosis in the fossa above the spina scapula. It passes over the joint capsule, under the acromion and coracoacromial arch and adheres to the upper part of the greater tubercle. It is innervated by the suprascapular nerve arising from the C4-C6 roots (11, 12). It makes the shoulder abduct. It makes maximum contraction at 30º elevation (13). It is the most important muscle of the rotator cuff and the most commonly injured muscle (14). M.infraspinatus starts from the fossa infraspinatus on the posterior aspect of the scapula and adheres to the postero-lateral aspect of the tuberculum majus of the humerus. It is innervated by N. suprascapularis (C5-C6). It is one of the most important external rotators of the shoulder. 60-90% of external rotation is provided by this muscle (15, 16). M. subscapularis starts from the subscapular fossa, passes in front of the joint and attaches to the tuberculum minus. It is stimulated by N.subscapularis (C5-C6). It causes internal rotation of the shoulder and functions as a humeral head depressor (17). M. teres minor starts from the outer edge of the scapula and attaches to the tuberculum majus. Its main function is to cause external rotation of the arm. It is innervated by N. Axillaris (C5-C6) (18).

Socio-economic problems caused by neck and shoulder pain are high and may impair quality of life (19). In this study, we aimed to retrospectively investigate whether there is a relationship between herniation types and rotator cuff lesions in the etiology of neck and shoulder pain, which we frequently encounter in the clinic, with cervical and shoulder magnetic resonance imaging findings.

MATERIAL AND METHODS

In this retrospective study, 524 patients with both dominant extremity shoulder and cervical magnetic resonance examination obtained from the data processing unit of Duzce University Faculty of Medicine between 01.08.2009-01.08.2023 were evaluated. Before starting the study, the approval of Duzce University non-interventional health research ethics committee was obtained. (Decision Number: 2023/162-16/10/2023)

MRI images of the patients on the system and the examinations reported by the specialist radiologist were reviewed. Additional triggers at the time of MRI were reviewed and if they should be excluded from the study, they were not evaluated. From the reports available on the system, the type of herniation (bulging, protruding, sequestered, extruded) at which spine level and other biomechanical pathologies were noted. After the report was analysed, it was further checked by a specialist neurosurgeon and the data was entered. A similar road map was followed in shoulder assessment. From the reports available on the system, it was noted which rotator cuff muscle of the patients had pathology. Other biomechanical pathologies of the patient's shoulder were noted. After the report review, the data were checked and entered by the specialist orthopedist and physiotherapist working on the musculoskeletal system. The inclusion criteria for the study were as follows: both cervical MRI and dominant extremity shoulder MRI were taken in the system, the patient

had not undergone shoulder or disc surgery before and did not have any other systemic disease.

The study was planned as a single group and subgroup comparisons were also made depending on demographic characteristics. Age, gender, dominant extremity, height-weight-body mass index and radiological findings were also analysed in detail.

Statistical Analysis: Data obtained were analyzed with IBM SPSS v.22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) statistical package. Numerical data were expressed as mean and standard deviation, while frequency and percentage were used for categorical data. Categorical data were analyzed with the Pearson chi-square, Fisher's exact, or Fisher-Freeman-Halton test, as appropriate. A p-value of 0.05 was accepted as statistical significance level.

RESULTS

A total of 524 patients, 153 (29.2%) male and 371 (70.8%) female, with a mean age of 51.17±13.70 (range, 13-93) years were included in the study.

According to the statistical analysis of our study, 410 of the participants had supraspinatus pathology, 234 had infraspinatus pathology, 243 had subscapularis pathology, and 11 had teres minor pathology. In addition, a statistically significant relationship was found between other shoulder pathologies and herniations at the C4-C5 and C5-C6 disc level ($p<0.05$).

Statistically significant relationship was found between supraspinatus pathology and disc herniations at the C4-C5 level according to Table 1 ($p<0.05$).

Table 1. Relationship between Supraspinatus Pathologies and Cervical Disc Pathology Grades

	No Supraspinatus Pathology (n=114)	**Supraspinatus Pathology Available (n=410)**	**p**
C2-C3, n (%)	8 (7.0)	53 (12.9)	0.082
C3-C4, n (%)	44 (38.6)	195 (47.6)	0.089
C4-C5, n (%)	53 (46.5)	255 (62.2)	**0.003**
C5-C6, n (%)	82 (71.9)	298 (72.7)	0.873
C6-C7, n (%)	54 (47.4)	226 (55.1)	0.142
Cervical Lordosis, n (%)	70 (61.4)	234 (57.1)	0.407
Other Pathologies, n (%)	100 (87.7)	371 (90.5)	0.386

According to Table 2, a statistically significant relationship was found between infraspinatus pathology and disc herniations at all cervical levels ($p<0.05$).

Table 2. Relationship between Infraspinatus Pathologies and Cervical Disc Pathology Grades

	No Infraspinatus Pathology (n=290)	**Infraspinatus Pathology Available (n=234)**	**p**
C2-C3, n (%)	25 (8.6)	36 (15.4)	**0.016**
C3-C4, n (%)	120 (41.4)	119 (50.9)	**0.030**
C4-C5, n (%)	148 (51.0)	160 (68.4)	**<0.001**
C5-C6, n (%)	196 (67.6)	184 (78.6)	**0.005**
C6-C7, n (%)	136 (46.9)	144 (61.5)	**0.001**
Cervical Lordosis, n (%)	166 (57.2)	138 (59.0)	0.689
Other Pathologies, n (%)	254 (87.6)	217 (92.7)	0.052

In Table 3, a statistically significant relationship was found between subscapularis pathology and herniations at the C4-C5 and C5-C6 disc level ($p<0.05$).

Table 3. Relationship between Subskapularis Pathologies and Cervical Disc Pathology Grades

	No Subskapularis Pathology (n=281)	**Subskapularis Pathology Available (n=243)**	**p**
C2-C3, n (%)	28 (10.0)	33 (13.6)	0.198
C3-C4, n (%)	123 (43.8)	116 (47.7)	0.364
C4-C5, n (%)	150 (53.4)	158 (65.0)	**0.007**
C5-C6, n (%)	191 (68.0)	189 (77.8)	**0.012**
C6-C7, n (%)	147 (52.3)	133 (54.7)	0.580
Cervical Lordosis, n (%)	165 (58.7)	139 (57.2)	0.726
Other Pathologies, n (%)	252 (89.7)	219 (90.1)	0.867

Statistically significant inverse relationship was found between therux minor pathology and herniations at C4-C5 disc level according to Table 4 ($p<0.05$).

Table 4. Relationship between Teres Minör Pathologies and Cervical Disc Pathology Grades

	No Teres Minör Pathology (n=513)	Teres Minör Pathology Available (n=11)	p
C2-C3, n (%)	58 (11.3)	3 (27.3)	0.126
C3-C4, n (%)	234 (45.6)	5 (45.5)	0.992
C4-C5, n (%)	306 (59.6)	2 (18.2)	**0.010**
C5-C6, n (%)	373 (72.7)	7 (63.6)	0.735
C6-C7, n (%)	274 (53.4)	6 (54.5)	0.941
Cervical Lordosis, n (%)	298 (58.1)	6 (54.5)	0.999
Other Pathologies, n (%)	460 (89.7)	11 (100)	0.316

Statistically significant relationship was found between other shoulder pathologies and herniations at C4-C5 and C5-C6 disc level according to Table 5 ($p<0.05$).

Table 5. Relationship between other pathologies of the shoulder and pathologies at cervical disc levels

	Other Pathology None (n=20)	Other Pathology available (n=504)	p
C2-C3, n (%)	1 (5.0)	60 (11.9)	0.494
C3-C4, n (%)	9 (45.0)	230 (45.6)	0.995
C4-C5, n (%)	6 (30.0)	302 (59.9)	**0.008**
C5-C6, n (%)	9 (45.0)	371 (73.6)	**0.005**
C6-C7, n (%)	7 (35.0)	273 (54.2)	0.092
Cervical Lordosis, n (%)	14 (70.0)	290 (57.5)	0.268
Other Pathologies, n (%)	16 (80.0)	455 (90.3)	0.247

DISCUSSION

It is known that cervical region pathologies may be a source of pain radiating to the shoulder and arm, but there is no conclusive evidence for this. The exact causes of the concept of pain, as stated in current scientific studies, have not been clearly established (20-22). In this case, scientific studies have led to the development and discussion of new concepts on pain. Shoulder complex and neck pain conditions are two different conditions that can be confused with each other. These two pains can be labelled together or they can be independent of each other. Sembrano et al. found that 37.4% of patients presenting to the spine clinic had neck and shoulder pain, compared to 0.6% of patients presenting to the shoulder clinic (23). In the literature, there are studies suggesting that the cause of shoulder pain is related to cervical nerve root irritation.(24) Our study is consistent with the literature and cervical disc herniations and rotator cuff pathologies affect each other.

Some scientists think that radiculopathy, especially affecting the C5 and C6 roots, may cause atrophy and weakness in the shoulder rotator cuff muscles and deltoid muscle in addition to pain and sensory changes.In some studies, it has been reported that pain in the shoulder and upper extremity are findings observed in the initial stage of cervical radiculopathy (25). Some opinions in the literature have emphasised that involvement of the lower cervical nerve roots innervating the shoulder circumference may be effective in the development of painful shoulder even if there is no clear evidence of cervical radiculopathy(26). In our study, we aimed to evaluate the relationship between cervical pathologies and shoulder rotator cuff pathologies with MRI findings.

When the cervical and shoulder MRI examinations of the patients included in our study who complained of pain radiating from the neck to the shoulder were analysed; cervical disc herniation was present in 90.3% of the patients, and cervical pathologies such as spondylosis, disc herniation, and cervical narrow canal were present in all other patients. Among the patients with pathology in the supraspinatus muscle, which is most frequently injured, 62.2.5% had C4-C5 disc herniation, while 72.7% had C5-C6 disc herniation. We think that the C4-C7 interval, which is the most mobile part of the spine, may degenerate more quickly and the supraspinatus, which it innervates, may be affected more quickly. Although pathologies in the infraspinatus and subscapularis muscles are statistically significantly associated with cervical disc herniations, we think that the causes of pain are more related to the variation of spine and muscle biomechanics from person to person. Teres minor pathologies are a pathology that we do not encounter very often in clinics, and the most important reason for this is explained by a strong muscle architecture (27). When the literature is examined, cervical disc herniations are most commonly seen in C4-C5 and C5-C6 discs (7).

We named the problems that may be mechanical in the spine and shoulder complex region as other pathologies and found that these pathologies are also related to the most mobile disc levels, C4-C5 and C5-C6 regions. In this case, we think that both regions should be understood by detailed examination together with anamnesis in patients with shoulder and neck problems in clinics. Because even though shoulder complex pathologies and cervical disc herniations are related to each other, we think that a broader perspective should be developed in the cause of pain and a treatment algorithm should be created with bio-psycho-social models.

A review of the literature shows that the most commonly affected muscle is the supraspinatus, followed by the infraspinatus muscle. The subscapularis and teres minor muscles are affected less frequently (28, 29). When we analysed all of our patients, the finding of supraspinatus muscle tear more frequently was consistent with the literature.

The limitations of our study are that the patient evaluations were made retrospectively and the compliance of the patients with clinical tests could not be performed. The findings of this study indicate that the complaints of patients with cervical and shoulder complex region MRI cannot always be explained and support the need for bio-psycho-social modelled treatment algorithms in this regard.

In conclusion, it should be kept in mind that the primary pathology in patients with shoulder pain may not belong to rotator cuff pathology or the primary cause may not be disc herniation in a patient presenting with cervical pain. It should be kept in mind that shoulder pain and shoulder-related pathologies can also be seen in a patient with cervical pain and the treatment algorithm should be created with a broad perspective.

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CASE REPORT

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Hidden Behind Chronic Dyspeptic Symptoms: Post-traumatic Diaphragmatic Eventration

ABSTRACT
Diaphragmatic eventration is commonly seen following high-energy traumas, particularly due to traffic accidents and falls from significant heights. This pathology has the potential to influence both the gastrointestinal and cardiorespiratory systems, presenting with a variety of symptoms. A 45-year-old male patient, with a history of trauma from falling off a tree, sought medical attention at our clinic with dyspeptic complaints and symptoms of shortness of breath. During the physical examination, diminished sounds were detected in the right lung field, along with epigastric tenderness. For diagnostic purposes, a posteroanterior chest radiograph (CXRs) and thoracic computed tomography (CT) scan were obtained. A subsequent bronchoscopy, performed with a pulmonology consultation, revealed decreased diaphragmatic movements. Taking into account the findings, a thoracic surgery treatment plan was devised for the patient. This case report underscores the significance of considering the seldom-encountered pathology of diaphragmatic eventration in patients presenting with dyspeptic and respiratory complaints. Keeping in mind that patients with such symptoms frequently turn to family physicians, it highlights the pivotal role of a multidisciplinary primary care approach in initiating the diagnostic trajectory.
Keywords: Family Medicine, Dyspepsia, Diaphragmatic Eventration.

Kronik Dispeptik Şikayetlerin Ardında Saklı Kalmış: Travma Sonrası Diyafragma Evantrasyonu

ÖZET
Diyafragma evantrasyonu, yüksek enerjili travmalarda, özellikle trafik kazaları ve yüksekten düşmelerde oluşmaktadır. Bu patoloji, gastrointestinal ve kardiyorespiratuvar sistemleri etkileyebilmekte ve semptomları değişkenlik gösterebilmektedir. Kırk beş yaşında erkek hasta, ağaçtan düşme travma öyküsü olup, dispeptik yakınmalar ve nefes darlığı semptomlarıyla polikliniğe başvurmuştur. Fizik muayenede, sağ akciğer seslerinde azalma ve epigastrik hassasiyet saptanmıştır. Tanı için posteroanterior akciğer grafisi (PAAC) ve toraks bilgisayarlı tomografisi (BT) çekilmiştir. Göğüs hastalıkları konsültasyonu ile yapılan bronkoskopide diyafragma hareketlerinde azalma görülmüştür. Hastaya, bulgular doğrultusunda göğüs cerrahisiyle tedavi planı oluşturulmuştur. Bu olgu sunumu, dispeptik ve solunumsal şikayetleri olan hastalarda, nadir rastlanan diyafragma evantrasyonu patolojisinin göz önünde bulundurulmasının önemini vurgulamaktadır. Bu tarz yakınmalarla hastaların sıklıkla aile hekimliğine başvurduğu göz önüne alınırsa; multidisipliner bir yaklaşım sergileyen birinci basamağın, tanı sürecini başlatan oldukça değerli bir basamak olduğunun önemi ortaya konulmaktadır.
Anahtar Kelimeler: Aile Hekimliği, Dispepsi, Diafragma Evantrasyonu.

INTRODUCTION

Dyspepsia is well-recognized in medical literature as a complaint affecting millions of individuals (1). Characterized predominantly as symptoms of the upper gastrointestinal system, dyspepsia manifests as epigastric discomfort, bloating, early satiety, and postprandial fullness (1). It can significantly impair patients' daily quality of life and may necessitate prolonged therapeutic approaches.

While there are numerous causes of dyspepsia, one of the most common is termed functional dyspepsia, characterized by the onset of symptoms without a specific identifiable cause (2). Other etiologies include gastritis, peptic ulcers, gastroesophageal reflux disease, and gallstones (2). Occasionally, atypical and unexpected causes that can give rise to these symptoms are encountered.

The diaphragm is one of the most crucial muscles separating the thoracic and abdominal cavities. The preservation of its functional and anatomical integrity is critical for the proper functioning of the cardiorespiratory system (3). Traumatic diaphragmatic injuries, resulting from either blunt or penetrating thoracoabdominal traumas, are infrequently encountered (4). Diaphragmatic eventration refers to the abnormal elevation of the diaphragm due to congenital or acquired defects, atrophy, or paralysis of the muscle fibers. It signifies the herniation of abdominal organs into the thoracic cavity (5). It often progresses asymptomatically and is discovered incidentally (5). Diaphragmatic eventrations most commonly occur on the left side, with those occurring on the right generally leading to more severe complications (6).

Cardiac surgery, traumas, tumors, pathologies related to muscles and nerves, granulomatous diseases, and surgical interventions concerning the thymus gland are observed as the most common causative factors (7). However, in many cases, these causes cannot be identified. In such cases, it is often believed that viral infections lead to diaphragmatic elevation or eventration (8).

Most traumatic diaphragmatic injuries occur due to high-energy traumas, particularly as a result of traffic accidents and falls from significant heights (9). According to literature data, the global prevalence of such injuries ranges between 0.8% and 5% (10). Clinical symptoms can vary depending on the location and size of the injury as well as the organs involved. These injuries can present with severe symptoms in the acute phase, or sometimes manifest with chronic symptoms that persist for months (11). In the chronic phase, clinical presentations may include atypical symptoms such as postprandial indigestion, bloating, and shortness of breath (11). Additionally, they can lead to various complications in the respiratory and digestive systems. Rare conditions like post-traumatic diaphragmatic eventration can emerge as easily overlooked underlying causes for the aforementioned symptoms.

Radiological examinations hold significant importance in the diagnosis. The evaluation process, which starts with direct radiographs, is detailed with computed tomography in suspicious cases (12). In this case study, the objective is to contribute to the existing literature by examining the epidemiological, clinical, diagnostic, and therapeutic approaches of diaphragmatic eventration that developed post-trauma, using a case that presented with chronic dyspeptic and respiratory complaints.

CASE REPORT

Case Presentation A 45-year-old male patient presented to our clinic with complaints of bloating, indigestion, upper abdominal pain, and occasional pronounced shortness of breath that had been persisting for the past 6-7 months. The patient reported that his dyspeptic symptoms intensified after meals and occasionally experienced a sensation of pressure in his chest along with the shortness of breath. He mentioned that these symptoms negatively impacted his daily activities and work performance. It was learned that the patient had contracted COVID-19 about three months prior but did not seek medical attention. Upon further inquiry into his medical history, the patient shared a 40 pack-year smoking history but had quit smoking 17 years ago. Upon detailed anamnesis, he revealed a trauma due to falling from a tree eight months ago. Since he did not experience any significant pain or symptoms immediately after the incident, he did not seek medical care. However, it was ascertained that he began experiencing symptoms about 2 months post the incident but did not associate his complaints with the post-fall trauma, which resulted in a delay in seeking medical assistance. He confirmed that he had not previously sought medical attention for his shortness of breath and dyspeptic symptoms. The decision to consult was made upon noticing a progressive worsening of his complaints in recent times.

Upon physical examination, mild tenderness was detected in the patient's epigastric region. Respiratory examination revealed a reduction in breath sounds on the right side, with diminished participation in respiration compared to the left side. Auscultation did not identify any significant crackles or rhonchi; however, coarse breath sounds were noted. Oxygen saturation (SpO2) measured using a fingertip pulse oximeter was 96%.

For the initial diagnostic evaluation, a posteroanterior chest radiograph (CXRs) was ordered for the patient (Figure 1). The CXRs revealed a notable elevation in the right diaphragm. Based on this finding, a thoracic CT scan was requested for the patient. The results of the thoracic CT indicated that the right hemidiaphragm was

positioned higher due to liver eventration, atelectasis had developed in the right lung's middle lobe due to compression, a reduction in lung volume was observed, and the right atrium was compressed (Figure 2).

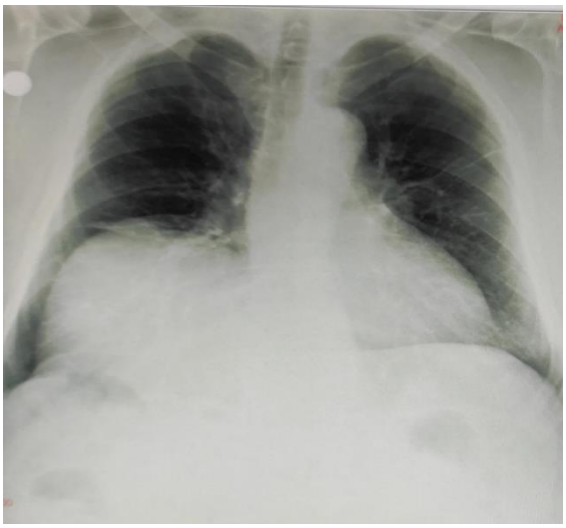

Figure 1. Posteroanterior Chest Radiograph (CXRs)

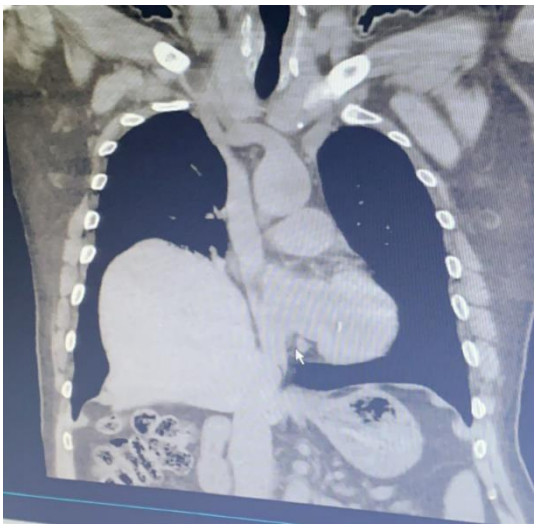

Figure 2. Thoracic Computed Tomography (CT)

In light of these findings, the patient was consulted with the department of chest diseases. At the chest diseases clinic, the patient underwent bronchoscopy under fluoroscopy and a respiratory function test. The evaluation of the respiratory function test indicated results in favor of a restrictive pathology. During bronchoscopy, it was observed that there was a reduction in diaphragmatic movements with respiration.

Based on these findings, the patient was referred for a thoracic surgery consultation. The thoracic surgeon assessed the patient's condition and established an appropriate surgical treatment plan. Due to the patient's pronounced symptoms, which significantly affected his quality of life, and the high risk of complications developing in the future, it was decided to perform a surgical plication procedure on the patient.

DISCUSSION

Diaphragmatic eventration is a clinical issue where intra-abdominal organs are shifted into the thoracic cavity due to the weakening or paralysis of muscle fibers (3). Though commonly seen in children, this condition is quite rare among adults (13). Often occurring in the right diaphragm, this disease usually presents without symptoms (14).

More than half of adult cases with unilateral diaphragmatic eventration are asymptomatic (8). In the remaining cases, symptoms such as exercise dyspnea, general muscle fatigue, chest pain, cough, and resting dyspnea can be observed (8). Our patient's increase in symptoms with positional changes and exercise is consistent with the literature. Unilateral diaphragmatic eventration in adults often goes unnoticed as it doesn't always lead to respiratory symptoms, and is generally identified incidentally. The detection of a unilateral diaphragm in a higher position in the posteroanterior lung radiograph typically prompts this diagnosis. Paradoxical movement of the diaphragm observed during inhalation with fluoroscopy (the sniff test) is usually diagnostic.

According to the literature, traumatic diaphragmatic injuries typically occur in high-energy traumas and most frequently on the left side (15). However, in our case, there was an eventration of the diaphragm on the right side, which brings into consideration a higher risk of serious complications. Furthermore, the fact that the patient's trauma resulted from a fall from height aligns with the literature.

In the case, the approach to the importance of radiological examinations has been consistent with the literature. The initial assessment with posteroanterior chest radiography (CXRs) was later detailed with tomography. This approach is typically recommended in the literature (16).

Whether the elevation of the diaphragm is due to paralysis or eventration is not crucial for treatment; its value lies only in clarifying the etiology (16). If desired, the presence of paradoxical movement in the diaphragm can be investigated with fluoroscopy (8). To illuminate the etiology, differentiate the diagnosis, rule out other pathologies, and ascertain the degree of the clinical picture, standard chest radiography, thoracic computed tomography, respiratory function tests, and other examinations can be conducted in conjunction with the patient's history (16). If required, the elevation due to eventration can also be calculated in direct and lateral chest radiographs (17). In the computed tomography scan, since the patient is lying down, the eventration becomes more pronounced, and the gas-filled stomach and intestines are better visualized (17).

Even if this pathology does not manifest any symptoms or signs, given the low rate of spontaneous recovery, it should be evaluated for surgery upon detection to protect the patient from potential side effects and problems that may arise in the future (5). The most critical surgical operation indication is the presence of respiratory restriction in the patient, confirmed with respiratory function tests (5). In adult patients with unilateral diaphragm paralysis or eventration, surgical plication is only indicated when there are symptoms (5). Although the etiologies of diaphragm paralysis and eventration differ, their pathophysiologies are similar, and both pathologies are repaired with the same surgical method (17). The aim of surgical plication is to prevent paradoxical movement during inspiration by tensioning and stabilizing the atrophied, thin, relaxed, and elevated diaphragm (17). In patients with symptomatic unilateral diaphragm paralysis or eventration, plication prevents the abdominal organs from shifting to the ipsilateral thorax and epigastric region during inspiration (18). This provides sufficient intrathoracic negative pressure for the expansion of the contralateral lung, enabling the correction of atelectasis and intrapulmonary shunts. Moreover, the pressure on the epigastric region is reduced, alleviating dyspeptic complaints (18). Not only does the patient gain better exercise performance and lung function, but the burden on the gastrointestinal system is also reduced.

CONCLUSION

Chronic dyspeptic complaints are a common symptom with numerous potential etiologies. However, when taking a detailed history from patients presenting with such symptoms, even though rare, serious causes like post-traumatic diaphragmatic eventration can be identified. In such atypical cases, early and accurate diagnosis can significantly improve the patient's quality of life.

Primary care family medicine represents a crucial point where patients first present with a wide range of health concerns. General symptoms, such as dyspeptic and respiratory complaints, can be directed towards more specific diagnoses through the detailed history-taking and physical examination by the family physician. This case once again underscores the role of family medicine as the first and most critical step in the multidisciplinary approach within the healthcare system.

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CASE REPORT

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Acute Arterial Thrombosis Following Chemoterapy in Patient with Oral Cavity Carcinoma- Importance of Decision Making in Family Medicine Practice- A Case Report

ABSTRACT

Oral cancer is most common in developing countries, but is also seen in the rest of the world. Patients with tumors have a higher risk of thrombosis, assuming that the underlying pathophysiological mechanism is endothelial dysfunction. The presented case describes the development of acute vascular thrombosis in a patient with late diagnosed carcinoma after a consecutive chemotherapy. A 62-year-old man was diagnosed with squamous cell carcinoma of the floor of the oral cavity, with subsequent surgical resection, radiotherapy and chemotherapy with cisplatin, 5-fluorouracil and cetuximab were followed. 2 days after the last infusion, acute peripheral arterial thrombosis was developed. Cancer and antitumor therapy exert a synergistic effect on coagulation activation. A probable toxic damage to the vascular endothelium leads to a decreased expression of nitric oxide synthetase and, accordingly, vasodilation, a decrease in anticoagulants and an increase in the levels of procoagulants such as tissue factor, which activates coagulation and induces the activation of platelets. The general practitioner occupies a central role in the health care system in a number of countries. In order to be able to perform its complex activities and successfully solve diverse health problems it is necessary to possess specific knowledge and skills from various fields of medicine.

Keywords: Squamous Cell Carcinoma, Thrombotic Complications, General Practitioner, Primary Care.

Ağız Kavitesi Karsinomlu Hastada Kemoterapi Sonrası Akut Arteriyel Tromboz-Aile Hekimliği Uygulamasında Karar Vermenin Önemi-Olgu Sunumu

ÖZET

Ağız kanseri en çok gelişmekte olan ülkelerde görülmekle birlikte dünyanın geri kalanında da görülmektedir. Altta yatan patofizyolojik mekanizmanın endotel disfonksiyonu olduğu varsayıldığında, tümörlü hastalarda tromboz riski daha yüksektir. Sunulan olguda, geç tanı alan karsinomlu bir hastada ardışık kemoterapi sonrasında gelişen akut vasküler tromboz anlatılmaktadır. 62 yaşındaki bir erkeğe ağız boşluğu tabanında skuamöz hücreli karsinom tanısı konuldu ve ardından cerrahi rezeksiyon, radyoterapi ve sisplatin, 5-florourasil ve setuksimab ile kemoterapi uygulandı. Son infüzyondan 2 gün sonra akut periferik arter trombozu gelişti. Kanser ve antitümör tedavisi pıhtılaşma aktivasyonu üzerinde sinerjistik bir etki gösterir. Vasküler endotelde olası bir toksik hasar, nitrik oksit sentetaz ekspresyonunun azalmasına ve buna bağlı olarak vazodilatasyona, antikoagülanların azalmasına ve pıhtılaşmayı aktive eden ve trombositlerin aktivasyonunu indükleyen doku faktörü gibi prokoagülanların seviyelerinde artışa yol açar. Pratisyen hekim birçok ülkede sağlık bakım sisteminde merkezi bir role sahiptir. Karmaşık faaliyetlerini gerçekleştirebilmek ve çeşitli sağlık sorunlarını başarıyla çözebilmek için tıbbın çeşitli alanlarından özel bilgi ve becerilere sahip olmak gerekir.

Anahtar Kelimeler: Skuamöz Hücreli Karsinom, Trombotik Komplikasyonlar, Pratisyen Hekim, Birinci Basamak Sağlık Hizmeti.

CASE PRESENTATION

A 62-year-old man, smoker for over 40 years, in October 2018 noticed a sore under the tongue. He visited his general practitioner (GP) who performed physical examination and local inspection of the oral cavity. He found ulceration under the tongue and concluded that it is a result of injury due to consumption of solid food. The doctor prescribed local therapy with gel containing glycerol-oxide-triester (TGO) in order to create a film that protects the wound from external mechanical and chemical irritations and stimulates the regeneration of the surrounding cells. In December of the same year, complaints of difficulty speaking and eating, difficulty in moving the tongue and loss of body weight appeared. After second examination by a general practitioner which revealed bigger pathological formation, he was referred and hospitalized in a maxillofacial surgery clinic. The local oral status revealed an ulcero-infiltrative lesion located in the anterior part of the floor of the oral cavity, involving the anterior third and the underlying soft tissues, as well as the ventral surface of the tongue. The neighboring teeth were of the third degree of mobility and with suspicion of lingual alveolar invasion in the area next to the premolars bilaterally. Local extraoral status revealed bilaterally enlarged lymph nodes with a size of about 2 cm. which were palpated in the right submandibular and in the left perimandibular site. A biopsy was performed, which demonstrated moderately differentiated squamous cell carcinoma of the floor of the oral cavity with massive regional lymph node metastases in extracapsular spread of the carcinoma. According to the TNM classification, T3M1Tx staging was accepted. Computed tomography (CT) revealed a tumor formation on the floor of the oral cavity with approximate dimensions of 40/40mm, involving part of the lower jaw and bilaterally enlarged perimandibular lymph nodes (Fig.1).

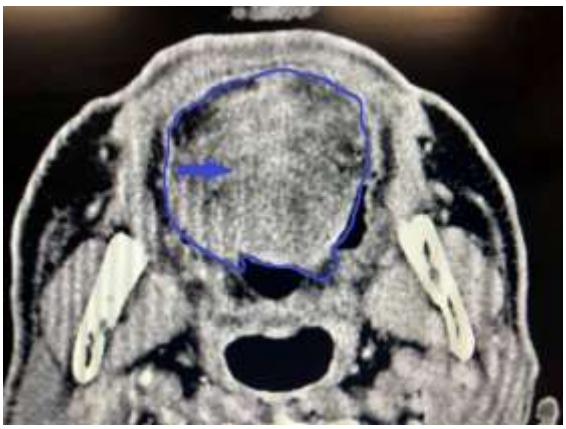

Figure 1. Computed tomograpgy showing tumor formation on the floor of the oral cavity

The laboratory indicators showed the typical for an oncological disease deviations - iron-deficiency anemia - reduced erythrocytes 3.1×10^{12}/l (normal range for males $4.2–6.2 \times 10^{12}$/l), hemoglobin 110g/l (normal range 140–180 g/l), hematocrit 0.27% (normal range 0.37%–0.55%), mean corpuscular volume 70 fl (MCV) [(normal range 82 – 98 fl)], iron 4.5 μmol/l (normal range for males 5.83-34.5 μmol/l), increased total iron-binding capacity 82.4 μmo/l) (TIBC) [(normal range 44.8-71.6 μmo/ l)] ; erythrocyte sedimentation rate (ESR) 60 mm/h (normal range for males1-15 mm/h), C-reactive protein (CRP) [(normal range 5–10 mg/l)]. After evaluation of the general and local status, as well as the results of the computed tomography, surgical treatment was initiated. Under general anesthesia with tracheal intubation, a radical bloc resection of the floor of the oral cavity, ventral surface of the tongue and cranial ½ of the height of the lower jaw, as well as bilateral selective cervical dissection was performed. Postoperatively, the patient was referred to a radiotherapy clinic, where radiotherapy was performed on the floor of the oral cavity and cervical chains on the right with a dose of up to 56 Gray and contralateral lymphatic chains on the left up to 50 Gray with the RapidARC technique in the period 01-03. 2019. In April 2023 due to complaints of a change in voice, difficulties in swallowing and breathing disorders, the patient was urgently admitted to the ear-nose-throat department. Local status revealed recurrence of tumor formation, and biopsy confirmed squamous cell carcinoma. A CT scan was performed which revealed a soft tissue lesion involving the left vocal fold, left thyroid cartilage, left aryepiglottic fold, left pharyngeal wall, and left partial epiglottis measuring approximately 40.1/19.2 mm. (Fig. 2).

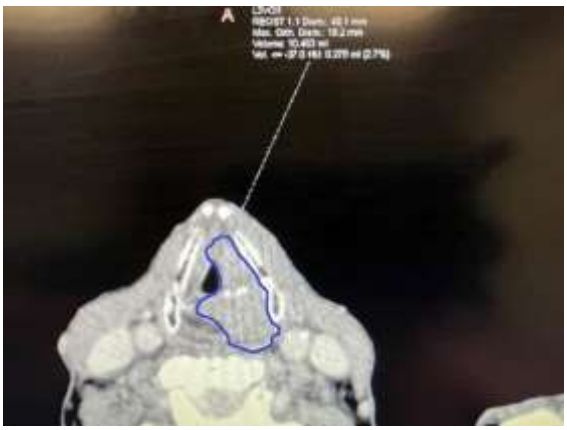

Figure 2. Computed tomography showing soft tissue lesion involving the left vocal fold, left thyroid cartilage, left aryepiglottic fold, left pharyngeal wall, and left partial epiglottis

Subsequent the positron emission computed tomography (PET-CT) showed an increased metabolic activity was visualized in the area of the soft palate, the laryngopharynx, the right half of the floor of the oral cavity (Fig. 3A, Fig. 3B) and a cervical lymph node on the left (Fig. 3C).

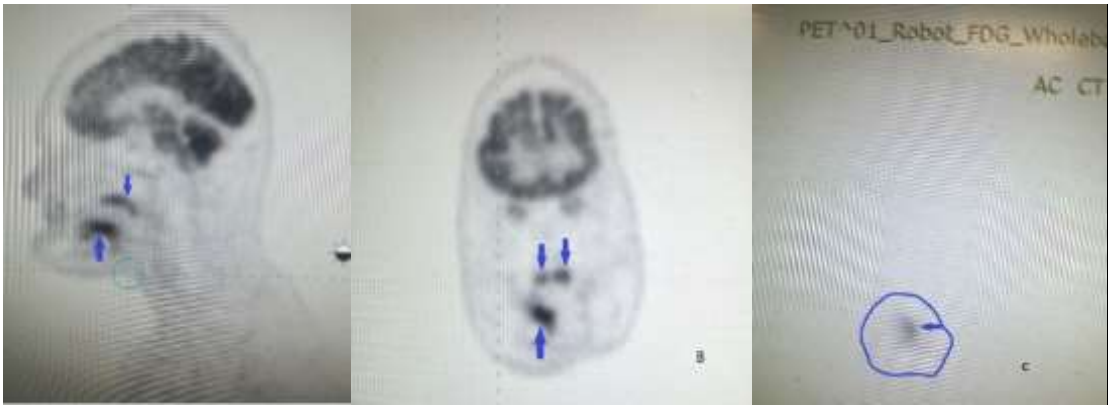

Figure 3. PET-CT showing Increased metabolic activity in the area of the soft palate, the laryngopharynx, the right half of the floor of the oral cavity (3A, 3B) and a cervical lymph node on the left (3C)

Surgical treatment followed, with a total laryngectomy performed, after which the patient was referred for 6 consecutive courses of chemotherapy, once a week. Combination treatment with cisplatin 100mg, 5-fluorouracil 700mg, cetuximab 300 mg in a single intravenous infusion with Ntrium chloride 0.9% 500 ml. and lipegfilgrastim 6mg. single subcutaneous injection. was started. He was discharged form hospital in 07. 2023 and 2 days later complaints of sudden severe pain in the right lower extremity occured. The patient approached his general practitioner by the phone and the initial treatment with nonsteroidal anti-inflammatory drugs was initiated. In several hours patient noticed pallor and coldness of the foot. Direct ambulatory consultation with the family doctor was provided who found weakened peripheral artery pulsations of the right lower extremity. According to these findings severe vascular complication was suspected. The patient was urgently referred and admitted to the vascular surgery department. Local status noted diminished palpable pulsations of the right femoral artery, absent distal, pale and cool foot. After a preoperative consultation with a cardiologist and an anesthesiologist, the surgical intervention was performed, during which it was established that the right common femoral artery was pulseless. Thrombendarterectomy (TEA) was performed, and the evacuated thrombus was cast-like (Fig. 4). Immediately after a strong pulse was restored and the patient was discharged from the operating room with stable hemodynamic parameters.

Figure 4. Thrombendarterectomy evacuated cast-like thrombus

DISCUSSION

Cancer of the oral cavity occurs more often in men, usually after 50 years of age. At the beginning of the disease, the clinical presentation is atypical and for a long time it is asymptomatic, which is why the diagnosis can be made late, when manifestations of involvement of adjacent structures or metastasis begin to dominate (1). Known premalignant lesions are leukoplakia and erythroplakia, which appear as white and red lesions, which requires a careful examination of the oral cavity by a dentist, otolaryngologist or general practitioner (2,3). These changes could be interpreted as inflammatory infiltrates or due to mechanical trauma, leading to possible diagnosis delay. Chemotherapy is a type of adjuvant therapy that is carried out with antitumor drugs, the most commonly used in oral cavity carcinomas being Cisplatin, Carboplatin, 5-fluorouracil (5-FU), Paclitaxel, Docetaxel, Hydroxyurea alone or in combination with other drugs (e.g. immunostimulators, targeted), which, however, leads to an increased risk of side effects, especially on the cardiovascular system. The two mechanisms by which the antineoplastic effect of these agents occurs are cytostatic (inhibition of cell division) and cytotoxic (destruction of the tumor cell) (4). Despite their targeted effect on the tumor, they also have a toxic effect on non-tumor cells by damaging them (5). An association with an increased risk of developing arterial and venous thrombosis has been established for some of the medications used for treatment. Platinum-based agents, such as **Cisplatin**, Carboplatin, Pyrimidine antagonists with representatives of **5-fluorouracil**, Gemcitabine, Anti-epidermal growth factor receptor antibodies ((EGFR)-**Cetuximab**, Bevacizumab) are included into this group (6,7). The exact mechanisms by which the development of thrombosis is not fully known. On the one hand, toxic damage to the vascular endothelium is assumed, which leads to a reduced expression of nitric oxide synthetase and, accordingly, vasodilation, and on the other, a decrease in anticoagulants and an increase in the levels of procoagulants such as tissue factor (TF), which activates coagulation. A third pathway of action involves the induction of platelet activation (8). Administration of 5-fluorouracil in rabbits has led to disruption of the endothelial monolayer, exposure of the subendothelial matrix, and

accumulation of platelet aggregates (9,10). Excessive EGF mediated cell growth are common in patients with a variety of malignancies, which is why antibody-based therapies that inhibit EGFR signaling, such as cetuximab, have been introduced. Patients treated with cetuximab are at a significantly higher risk of venous than arterial thrombosis, but studies are needed to clarify the reasons (11). Cancer is a separate risk factor for the occurrence of vascular thrombosis. Recently, there have been reported increasing number of arterial thrombotic events in cancer patients, which is associated with a 3-fold higher risk of death (12). Adverse vascular events include acute myocardial infarction or ischemia, stroke, peripheral or visceral thrombosis, which also determines the varied clinical presentation. Tumor cells can produce ligands including thrombin, adenosine diphosphate (ADP), thromboxane A2, metalloproteinases (MMPs) and TF. In response, the stimulation of platelet surface receptors (e.g., PAR-1 and PAR-4 receptors, P2Y12 receptor, and thromboxane receptor) can mediate platelet activation (13,14,). In addition, cancer cells can express procoagulant factors. Tissue factor is the receptor for factor VII and site of activation of factor VII and factor VIIA. TF results in activation of coagulation cascade when it comes into contact with activated factor VIIa resulting in local generation of thrombin, the most potent platelet activator. During apoptosis of tumor cells which might be induced by chemotherapeutic agents, procoagulant factors are released and fibrinolytic are reduced such as antithrombin, proteins C and S which can lead to the development of arterial thrombosis (15).

CONCLUSIONS

The presented clinical case demonstrates a patient with a rare tumor of the floor of the oral cavity diagnosed late which metastasized due to delay in initial diagnosis. Cancer and antitumor therapy exert a synergistic effect on coagulation activation. Further studies are needed to elucidate the exact mechanisms by which these life-threatening events occur, as well as the need and indications for anticoagulant therapy during and after treatment in this significant group of patients. The general practitioner occupies a central role in the health care system in a number of countries and is labeled as the "gate keeper" as he is responsible for navigation of patients through the other floors of the health care system. In order to be able to perform its complex activities and successfully solve diverse health problems of its patients, it is necessary to possess specific knowledge and skills from various fields of medicine. Their acquisition has a direct relationship with the quality of practical exercises during student training. Expanding training to include simulators would help to develop and to refine the sophisticated process of diagnostic thinking and decision making. The specialization in general medicine in Bulgaria must also adapt to the specific needs of practicing in primary care. Physicians may benefit from including oral surgery topics in the training program. continuing medical education plays a significant role, but it is necessary to have personal motivation and mandatory regulations by the state as well to increase quality of health care services carried out by the general practitioners.

Compliance with Ethics Requirements: The author declares no conflict of interest regarding this article.

The author declares that the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patient included in the study.

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