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RESEARCH ARTICLE

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This study has been presented as an oral presentation at the 21. International Eastern Mediterranean Family Medicine Congress held between 12-15 May 2022 in Adana, Turkey.

The Effect of a Mobile Phone Application on Smoking Cessation

ABSTRACT

Objective: The aim of this study was to investigate whether these applications are effective in quitting smoking by using one of the smartphone applications in addition to motivational interviewing in patients who applied for giving up smoking.

Methods: A randomized controlled intervention study was between January and July 2020. Adults aged 18-65 years who smoke at least one cigarette a day were included in the study. In the prospective study, the patients were followed for 6 months and a total of ten interviews were made. A phone application was installed on the intervention group. Afterwards, the smoking status of the patients was evaluated by telephone or face-to-face.

Results: Sixty-three smokers participated in the study. Fifty patients completed the study, 25 controls and 25 interventions. Long-term smoking cessation findings at the first, third and sixth months were evaluated for both groups. Of the patients, 64% in the intervention group and 32% of the patients in the control group quit smoking at the end of the first month. The success of quitting at the end of the first month was found to be statistically more significant in the intervention group than in the control group (p=0.024). Patients who did not continue smoking at the end of the sixth month were 44% in the intervention group and 24% in the control group, and there was no statistically significant difference between the two groups. Of the 50 patients, 16 had never smoked for six months.

Conclusions: The smartphone mobile-application showed a positive effect in promoting the increase in the smoking quitting rate. The intervention was found to be effective in 30-day smoking cessation success. Despite higher smoking quitting rates at 3 and 6 months, the application was not effective.

Keywords: Smoking Cessation, Motivational Interview, Phone Application.

Cep Telefonu Uygulamasının Sigara Bırakmaya Etkisi

ÖZET

Amaç: Bu çalışmanın amacı, sigarayı bırakmak için başvuran hastalarda motivasyonel görüşmeye ek olarak akıllı telefon uygulamalarından birini kullanarak bu uygulamaların sigarayı bırakmada etkili olup olmadığını araştırmaktır.

Gereç ve Yöntem: Ocak ve Temmuz 2020 arasında randomize kontrollü bir müdahale çalışması yapıldı. Çalışmaya günde en az bir sigara içen 18-65 yaş arası yetişkinler dahil edildi. Prospektif çalışmada hastalar 6 ay takip edilmiş ve toplam on görüşme yapılmıştır. Müdahale grubuna telefon uygulaması yüklendi. Daha sonra hastaların sigara içme durumları telefonla veya yüz yüze değerlendirildi.

Bulgular: Çalışmaya 63 sigara içicisi katıldı. Çalışmayı elli hasta, 25 kontrol ve 25 müdahale grubu olarak tamamladı. Her iki grup için de birinci, üçüncü ve altıncı aydaki uzun dönem sigara bırakma bulguları değerlendirildi. Müdahale grubundaki hastaların %64'ü, kontrol grubundaki hastaların %32'si birinci ay sonunda sigarayı bırakmıştır. Birinci ay sonundaki bırakma başarısı müdahale grubunda kontrol grubuna göre istatistiksel olarak daha anlamlı bulunmuştur(p=0,024). Altıncı ay sonunda sigaraya devam etmeyen hastalar müdahale grubunda %44, kontrol grubunda %24'dür ve her iki grup arasında istatistiksel olarak anlamlılık yoktur. Toplam 50 hastanın 16'si altı ay boyunca hiç sigara içmemiştir.

Sonuç: Akıllı telefon mobil uygulaması, sigara bırakma oranındaki artışı teşvik etmede olumlu bir etki göstermiştir. Müdahalenin 30 günlük sigara bırakma başarısında etkili olduğu bulundu. 3. ve 6. aylarda daha yüksek sigara bırakma oranlarına rağmen uygulama etkili olmadı.

Anahtar Kelimeler: Sigara Bırakma, Motivasyonel Görüşme, Telefon Uygulaması.

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INTRODUCTION

Smoking is one of the most important preventable causes of death in politics and in the world. One of the biggest problems today is nicotine dependence. Tobacco is one of the world's largest public health risks. Tobacco use and the various diseases it causes, cause the death of more than 8 million people in the world annually. While more than 7 million of these deaths are due to tobacco use, approximately 1.2 million are the result of exposure to second-hand smoke by non-smokers (1).

Compared to non-smokers, the relative death rate of smokers was tripled for men aged 45-64 and doubled for men aged 65-84 (2). Looking at the 2019 data of the Turkish Statistical Institute (TUIK), the rate of individuals aged 15 and over who smoke every day has increased from 26.5% in 2016 to 28% in 2019. This rate was determined as 41.3% for men and 14.9% for women. Every year, approximately 110 thousand people die due to smoking (3). Nicotine is the primary psychoactive stimulant, addictive substance in cigarettes. The tar contained in cigarettes increases the risk of lung cancer, each cigarette shortens human life by 11 minutes (4).

It is known that even when physicians ask patients about their smoking status and warn them not to smoke during their routine treatment services, it leads them to think about quitting smoking, and at a rate of 1-3% (5). It has been determined that physicians' advice and support in quitting smoking motivates many smokers and encourages them to try to quit. Physicians working in primary care have a great role in this regard (6).

The use of communication and mobile phone applications in health promotion is becoming more and more widespread. Since most relapses occur in the first weeks after a quit attempt, such interventions have the potential to provide support when it is most needed (7). Due to the high prevalence of smartphone use, providing health promotion interventions using smartphone apps is a promising approach, especially because of proximity to users, cost-effectiveness, location independence, possibility of adaptation, and immediate interactive support (8, 9).

The aim of this study was to investigate whether these applications are effective in smoking cessation by using one of the smartphone applications in addition to motivational interviewing.

MATERIAL AND METHODS

Patients between the ages of 18-65 who smoked at least one cigarette a day and wanted to quit smoking between January and July 2020 in the Erciyes University Faculty of Medicine Family Medicine Department polyclinic were included in the study. Patients who agreed to participate in the study signed the consent form. The study was approved by an Ethical Committee. The patients were followed for six months and the study ended in January 2021. The research is a randomized controlled intervention study. Randomization was performed according to admission sequence, one by one, first to study group than to control group. The intervention was carried out with the program called Beat Smoking, which was developed as a mobile phone application, and its effectiveness on smoking cessation was investigated.

Tools: In the study, informed consent form, personal information form, Fagerström Test for Nicotine Dependence and the form that was distributed to the patients including the motivational interview and behavioral changes used for the first interview were used. A questionnaire form including socio-demographic data such as name-surname, age, gender, education level, monthly income levels, marital status, and the number of cigarettes consumed per day, how many years have been smoked, whether they have been given smoking cessation advice, and the reason for wanting to quit if they are considering quitting smoking was used.

Fagerström Test for Nicotine Dependence (FTND): Fagerström first proposed the Fagerström Tolerance Test in 1978 to measure physical dependence on nicotine. This test was revived by Fagerström, Heatherton and Kazlowki in 1992 and the Fagerström Test for Nicotine Dependence emerged. This test consists of six questions and each question is given a different score. According to the total scores obtained, nicotine addiction was divided into five groups as very low (0-2 points), low (3-4 points), medium (5 points), high (6-7 points), and very high (8-10 points). It was adapted into Turkish by Uysal et al. in 2004 and a reliability study was conducted. In the study of Uysal et al., the reliability coefficient of the scale was reported as 0.56 (10, 11).

Properties of the Mobile Phone Application: The phone application we used in our study is the application called Beat Smoking. The interface of this program is beautifully designed, it is free for everyone to use, the login-registration to the application is quite simple and the application is useful. Many users find it difficult to maintain quitting during and after treatment. The most important reason for this is the loss of motivation. It is aimed that this application will increase the motivation needed and provide continuous support to the patient in quitting smoking.

In this program, the person first registers with their e-mail address. Then the person answers questions about the degree of addiction. According to these questions, the program measures the degree of addiction of the person and determines how long the desire to smoke will be. The person can track how often they need nicotine, thanks to the application. When the person wants to smoke, by clicking on the I want to smoke button, she is directed to the page containing the activities and suggestions (hiking, watching movies, etc.) that she can do instead of smoking. In addition, various scientific articles and articles about the harms of

smoking can be accessed in practice. It informs the patient about the changes that occur in the body from the moment the patient quits smoking. There are motivating notifications about how long he has not smoked during the day. If the patient does not quit smoking, he warns about what problems he will encounter in his life.

Inclusion Criteria:

• Those who smoke at least one cigarette every day for at least one year and who want to quit smoking
• Those between the ages of 18-65
• Those who read, accepted and signed the informed consent form
• Having completed the questionnaire and the Fagerström test completely
• Will not receive any other treatment for smoking cessation during the study
• Accepting 6-month follow-up
• Patients with Android phone users were included in the study.

Exclusion Criteria

• Those younger than 18 or older than 65
• Not accepting 6-month checks
• Those who quit smoking before applying to the outpatient clinic
• Not using an Android phone
• Patients taking active drug therapy to quit smoking were excluded from the study.

Study Design: This study was carried out in Erciyes University Faculty of Medicine Family Medicine Polyclinic. A randomized controlled trial was conducted. Sixty-three patients (over 18 years) who applied to quit smoking were divided into 2 groups. Patients were randomly assigned to an intervention group and a control group, respectively. Thirty-three patients were included in the control group and 30 patients were included in the intervention group.

Eight patients in the control group and five patients in the intervention group who could not be reached during the controls were excluded from the study. The patients who accepted the study signed the consent forms and filled the questionnaire form and FNAT. The control group was formed by interviewing the patients about motivational, behavioral and life changes, which lasted for about 30 minutes. In addition to motivational interview therapy, the other 25 patients were given a smart phone application called "Beat Smoking", and the intervention group was created, and the intervention group used the smart phone application every time they wanted to smoke during the day.

During the interviews, a quit date was determined to be within two weeks. If there is a special day in the recent history, it is recommended that patients choose that day in terms of motivation. In the interview, the reasons for change that are important for the patients were discussed. The interview is about their private reasons and the personal benefits of changing their behavior that are not judgmental and non-confrontational. Reminding the harms of cigarette consumption, speeches were made about obstacles. Behavioral and lifestyle changes were also recommended to patients.

After determining the quit date for each patient, smoking cessation status was evaluated by telephone or face-to-face interviews. The patients were informed at each interview, they were encouraged to quit smoking, and the importance of this issue was repeatedly explained to the patients. Patients were interviewed once a week for the first month. In the second month, smoking cessation status was followed for 6 months by interviewing every 2 weeks and then monthly. A total of 10 interviews were conducted with the patients and the number of cigarettes smoked was recorded.

Statistical Analysis: SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). Chi-square and Fisher's exact tests were used to analyze categorical expressions. Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Mann-Whitney-u test was used in paired group analysis for parameters that did not show normal distribution. Spearman correlation analysis was used to analyze the relationship between continuous measurements. Statistical significance level was taken as $p<0.05$ in all tests.

RESULTS

A total of 63 patients, 30 in the intervention group and 33 in the control group, were included in the study. Among these patients, 5 patients in the intervention group and 8 patients in the control group could not be reached during the controls, so the patients were excluded from the study. When the socio-demographic data of the patients included in the study were examined, the mean age of the participants was 40.58 (SD:12.5). 31 (62%) of these participants were under 45 years old, 14 of them were between 45 and 55 years old, and five of them were between 55-65 years old. The majority of the participants were aged 40 (54%) and below.

Thirty-six percent of the participants were female and 64% were male. Seventy percent of them were married and 68.6% of the married participants were men. Of the singles 46.7% were female participants. 42% of them were college graduates. 71.4% of college graduates were male. Eight (66.6%) of the primary school graduates were female and four (33%) were male. The number of participants who did not work in any job consisted of 18 people. Nine (50%) were female and nine (50%) were male. Although four of them were retired and had a certain income, all of them were men. The income level of 38% of the participants was 3500 TL and above. When the intervention and control groups were compared, there was no

statistically significant difference between the groups in terms of gender, marital status, educational status, employment status, income status and age (Table 1).

Table 1. Evaluation of the demographic characteristics of the patients and the differences between the groups

	Intervention	**Control**	**Total**	**p**
	n (%)	**n(%)**	**n(%)**	
Gender				
Women	11 (44)	7 (28)	18 (36)	0.239
Men	14 (56)	18 (72)	32 (64)	
Marital Status				
Single	6 (24)	9 (36)	15 (30)	0.355
Married	19 (76)	16 (64)	35 (70)	
Education				
Elementary school	6 (24)	6 (24)	12 (24)	0.771
Secondary school	3 (12)	1 (4)	4 (8)	
High school	6 (24)	7 (28)	13 (26)	
University and higher	10 (40)	11 (44)	21 (42)	
Working status				
Unemployed	7 (28)	11 (44)	18 (36)	0.239
Working	18 (72)	14 (56)	32 (64)	
Income				
Less than 2000 TL	9 (36)	8 (32)	17 (34)	0.664
2000-3500	8 (32)	6 (24)	14 (28)	
Over 3500	8 (32)	11 (44)	19 (38)	
	Intervention	Control	Total	
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
Age	40 (19-60)	37 (18-64)	40 (18-64)	0.705

* p<0,05, Chi-square and Fisher exact test, Mann Whitney-U test=Median (Min-Max)

According to the Fagerström Test for Nicotine Dependence (FTND), the mean addiction score in the sample was 4.22 ± 2.65 points. The mean FTND value of the case group was 4.16 points, and the mean FTND value of the control group was 4.04 points. There was no significant difference between the two groups in terms of FTND scores. Evaluation of the degree of addiction is divided into five classes (0-2= very little dependence, 3-4= little dependence, 5=moderate dependence, 6-7= high degree of dependence, and 8-10=very high degree of dependence) as applied in clinical practice. In the evaluation of addiction degrees according to FTND, the rate of very little, little, and highly dependent (7 people each) was the same in the case group, while the rate of highly dependent (9 people) was found to be higher in the control group. However, no significant finding was found in the differences between the FTND scores of the patients and the groups.

The FTND scores of the intervention and control groups and their smoking cessation status at the first, second and third months were evaluated. The median FTND score was 5 for those who quit smoking in the first month, 4.5 for those who quit at the third month, and 4 for those who quit at the sixth month. In our study, the degree of dependence according to FTND did not affect the success of smoking cessation in both groups. It was determined that the differences between FTND scale scores and smoking cessation in the first, third and sixth months were not statistically significant (Table 2).

Table 2. Comparison of patients' smoking cessation and FTND scores

	First month		**Third month**		**Sixth month**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
FTND score	4 (0-7)	5 (0-10)	4,5 (0-7)	4,5 (0-10)	5 (0-7)	4 (0-10)
p	0.314		0.688		0.812	

* p<0,05, Mann Whitney-U test=Med (Min-Max)

In the intervention group 64% of the patients and 32% of the patients in the control group quit smoking at the end of the first month. The success of quitting at the end of the first month was found to be statistically more significant in the intervention group than in the control group (p=0.024). At the end of the third month, 56% of the intervention group still did not smoke, while this rate was 32% in the control group. Although the rate of those who quit smoking was higher in the intervention group, it was not statistically significant. Patients who did not continue smoking at the end of the sixth month were 44% in the intervention group and 24% in the control group, and there was no statistically significant difference between the two groups. Of the 50 patients, 16 never smoked for six months (Table 3).

Table 3. Evaluation of the patients' first month, third and sixth month smoking cessation findings and the differences between the groups

Quit smoking	Intervention	Control	Total	p
	n(%)	n(%)	n(%)	
First month				
Yes	16 (64)	8 (32)	24 (48)	**0.024**
No	9 (36)	17 (68)	26 (52)	
Third month				
Yes	14 (56)	8 (32)	22 (44)	0.087
No	11 (44)	17 (68)	28 (56)	
Sixth month				
Yes	10 (44)	6 (24)	16 (32)	0.225
No	15(56)	19 (76)	34 (68)	

* p<0,05, Chi-square and Fisher exact test

In the first month follow-up of the study, 66.7% of women quit smoking in the intervention and control groups, while it was 37.5% in men. In terms of gender, women quit smoking at a higher rate than men in the first month (p= 0.048). Among the age groups, the highest quitting success was in the 55-65 age group (60.0%), while the 18-24 age group (16.6%) achieved the lowest success.

There was no statistically significant difference between age groups in terms of success. According to educational status, smoking cessation success was found to be close to each other in primary school (58.3%), secondary school (50%) and high school (53.8%), while the success rate was 38.1% in the university and higher education group. There was no statistically significant difference in success between the education groups. In the first month follow-up, the quit rates of married and single individuals were found to be very close to each other and no difference was observed between the groups (Table 4).

Table 4. Comparison of patients' quit success at the end of the first month in terms of sociodemographic characteristics

	Successful	Unsuccessful	P
	n(%)	n(%)	
Gender			
Women	12 (66.7)	6 (33.3)	**0.048**
Men	12 (37.5)	20 (62.5)	
Marital Status			
Single	7 (46.7)	8 (53.3)	0.902
Married	17 (48.6)	18 (51.4)	
Education			
Elementary school	7 (58.3)	5 (41.7)	
Secondary school	2 (50)	2 (50)	0.686
High school	7 (53.8)	6(46.2)	
University and higher	8 (38.1)	13 (61.9)	
Working status			
Unemployed	9 (50)	9 (50)	0.832
Working	15 (46.9)	17 (53.1)	
Income			
Less than 2000 TL	9 (52.9)	8 (47.1)	
2000-3500	9 (64.3)	5 (35.7)	0,157
Over 3500	6 (31.6)	13 (68.4)	
Age			
18-24	1(16,6)	5(83,4)	
25-34	5(55,5)	4(44,5)	
35-44	8(50)	8(50)	0.753
45-54	7(50)	7(50)	
55 and over	3(60)	2(40)	
Number of cigarettes consumed per day			
10 and less	8 (57.1)	6(42.9)	
11-20	16 (50)	16 (50)	0.303
21-30	0 (0)	3 (100)	
31 and more	0(0)	1(100)	
Presence of other smokers in the house			
Yes	9 (36)	16 (64)	0.089
No	15 (60)	10 (40)	
Receiving advice to quit smoking by the physician			
Yes	13 (48.1)	14 (51.9)	0.982
No	11 (47.8)	12 (52.2)	

* p<0,05, Chi-square and Fisher exact test

In the third month follow-up of the study, the success of smoking cessation was 61.1% for women in the total intervention and control groups, while it was 34.4% for men. There was no difference in the success of quitting according to gender in the third month follow-up. Among the age groups, the highest quitting success was in the 55-65 age group (60.0%), while the 18-24 age group (16.6%) achieved the lowest success. There was no statistically significant difference between age groups in terms of success. When the relationship between income status and smoking cessation was examined, higher quitting success was observed in those with income status of 3500 TL and below (p= 0.031). In the first month follow-up, the quit success rates of married and single people were found to be very close to each other and no difference was observed between the groups. No statistically significant difference was found between the other parameters and the success of quitting smoking at the third month.

In the sixth month follow-up of the study, the success of quitting smoking was found to be 55.6% for women in the total intervention and control group, while it was 21.9% for men. In terms of gender, the success of quitting smoking was found to be significantly higher in women in the sixth-month follow-up (p= 0.016).

Among the age groups, the highest quitting success was in the 55-65 age group (60.0%), while the 18-24 age group (16.6%) achieved the lowest success. There was no statistically significant difference between age groups in terms of success. No statistically significant difference was found between the other parameters and the success of quitting smoking at the sixth month.

DISCUSSION

Statement of Principal Findings: Of the patients, 64% in the intervention group and 32% of the patients in the control group quit smoking at the end of the first month. The success of quitting at the end of the first month was found to be statistically more significant in the intervention group than in the control group (p=0.024). Patients who did not continue smoking at the end of the sixth month were 44% in the intervention group and 24% in the control group, and there was no statistically significant difference between the two groups. Of the 50 patients, 16 had never smoked for six months. Smoking cessation intervention with Beat Smoking was found to be effective on 30-day smoking cessation success, but not on longer (3 months and 6 months) quitting success. Being in the intervention group in the first month increased success 2 times, at the third month 1.75 times, and at the sixth month 1.6 times.

Comparison with the Existing Literature: Bindhim et al. in their randomized controlled study with 684 participants, a smartphone decision aid application with support features and an information-only application were compared. The intervention included mandatory information on smoking cessation options, benefits and harms, as well as push notifications from the study server and daily motivational messages. The control application contained non-essential information about withdrawal options, benefits and harms, similar to those found in the intervention application. It did not provide any structured process for evaluating the options, benefits, and harms of quit methods, nor did it provide ongoing support for adhering to the decision to quit. As a result of this study, only information was available at the first (28.5% vs. 16.9%), third (23.8% vs. 10.2%) and sixth (10.2% vs. 4.8%) months. It was found that the intervention group was more likely to abstain from smoking compared to the application that included it (12). The phone application we used was also an application containing more information, but it also suggested additional activities that can be done when smoking is desired. There were no motivational messages sent daily. The absence of notifications required the participant to willingly enter the practice. Although there was no statistical significance in the third and sixth months, we achieved higher smoking cessation percentages in the first month (64% vs. 32%), the third month (56% vs. 32%), and the sixth month (44% vs. 24%). Compared to this study, our participants quit smoking at a much higher rate. The features of the phone application may be insufficient for long-term smoking cessation. Motivational interviews with both groups over the phone or face-to-face at regular intervals may have increased the dropout percentages of the total participants.

Whittaker et al., in a systematic review conducted in 2016, examined 12 studies with a six-month smoking cessation output and found that mobile phone-based interventions increased smoking cessation success 1.67 (1.46 - 1.90) times (13).

Graham et al. conducted a systematic review and meta-analysis of 40 studies that included internet interventions for adult smoking cessation. In the study, interactive internet interventions were found to be 2.10 (1.25-3.52) times more effective than smoking cessation interventions with printed materials. No significant results were obtained when static internet interventions were compared with printed materials (14). In our study, it was observed that the intervention increased the success rate in the first month by 2 times, similar to interactive internet interventions. Unlike this study, our phone application did not contain active motivational messages. However, we think that the use of a phone application and motivational interviews with weekly follow-ups in the first month may have increased our success, similar to this meta-analysis.

Vidrine et al. in a randomized study conducted with 95 participants in HIV-positive patients, participants who received mobile phone intervention were found to be 3.6 times more likely to quit smoking than participants who received

normal care (15). Personally designed mobile phone applications for those with chronic diseases can be more helpful in quitting smoking.

In a randomized study of 1865 people examining the effect of online interventions containing motivational or action-oriented information to quit smoking, the 7-day point prevalence of smoking cessation at 2, 6, and 12 months (no smoking in the last 7 days) was found to be significant only at 6 months (16). This may be due to the fact that the online intervention used, unlike our study, was defined specifically for the individual. In addition, we evaluated long-term smoking cessation rates (3 months and 6 months), not point prevalence. The phone application may have been insufficient to maintain long-term withdrawal. It may be more useful to identify the "active ingredients" that make Internet-based smoking cessation programs more effective to these applications.

In the thesis study conducted at Ege University Health Sciences Institute in 2017, the WhatsApp application, which was integrated into standard outpatient services, was used. Fifty percent of 130 individuals reached at the end of the first month; at the end of the third month, 38.3% of the 128 individuals reached were successful in quitting smoking (17). In our study, the success rate of 48% in the first month and 40% in the third month is similar to this study. However, during our study, the covid-19 pandemic broke out and follow-up interviews with the patients had to be made mostly via telephone. In addition, the motivation of the patients was also affected due to the quarantine conditions. This situation may have reduced our quit success.

In the study conducted by Kaur Ubhi et al., using the SmokeFree28 (SF28) phone application and investigating the effects of the application on smoking cessation, 1170 people were included in the study and their 28-day smoking cessation rates were examined. However, not all of the participants used the application every day and the rate of quitting was found to be higher in those who used it. The rate of those who did not smoke for 28 days or longer was found to be 18.9%. This study concluded that SF28 may help some smokers quit (18). Similarly, we found significance in the intervention group at the end of the first month. In our study, first month dropout rates were higher in both groups.

Strengths and Limitations of the Study: Data collection and interviews with the patient were carried out by a single researcher, and the motivational interview was written down on paper and transferred to the patients so that it could be applied to each patient in a similar way. Thus, a standardization was achieved by avoiding the differences depending on the physicians in the interviews. With telephone and face-to-face interviews, it was ensured that the participants used the application and their adaptation to the study was increased. Beat Smoking smartphone application is an application for smoking cessation in Turkey, which is used in Turkish and provides evidence-based information and content. In addition to similar mobile applications that are still in use in the world, it is also advantageous that it offers additional suggestions that a person can enter when he/she wants to smoke.

One of the limitations of this study is that smoking cessation was self-reported and not biochemically validated. In addition, there is no remote access to the application, where we can evaluate whether the patients use the application or not. It is reported via self-report; as automatic recording of usage data is not possible. Another limitation is the 6-month follow-up of smokers. After 6 months, recurrences can be seen up to a year. This will need to be addressed in the future development and evaluation phase. The decrease in the number of patients at the beginning of our study may have reduced the power of the study, as the patients did not want to spend a long time in the hospital due to the COVID-19 pandemic.

CONCLUSION

Smartphone applications for smoking cessation are increasingly used worldwide. Although there are many phone apps for quitting smoking on the market, few studies have evaluated their effectiveness. For this reason, there is a need for more studies on the use of smartphones in smoking cessation in our country.

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RESEARCH ARTICLE

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Determining the Vasohibin-1 Levels of the Serum and Broncoalveolar Lavage Fluid in the Patients with Lung Cancer

ABSTRACT

Objective: Lung cancer constitutes 17% of all cancer cases and accounts for 23% of the deaths caused by cancer all over the world. Vasohibin-1 (VASH-1) is an angiogenesis-inhibiting factor synthesized by endothelial cells (ECs). This study aimed to examine the VASH-1 levels of the bronchoalveolar lavage (BAL) and serum in the patients with lung cancer.

Methods: A total of 82 patients participated in this study. 39 and 43 of them had a benign lung disease and lung cancer, respectively. The VASH-1 levels of serum and BAL were measured using the Enzyme-Linked Immunosorbent Assay (ELISA).

Results: The BAL VASH-1 levels of the patients in the lung cancer group were found to be statistically significantly lower than those of the patients in the benign lung disease group (p=0.032). No statistically significant difference was found between the individuals with lung cancer and benign lung disease in terms of the serum VASH-1 concentration (p=0.206). A statistically significantly moderate positive correlation was found between the serum and BAL VASH-1 levels in the benign and malignant cases (benign r=0.442, p=0.005; malignant r=0.364, p=0.016). When the lung cancer patients were categorized into pathological stages and histological types, no significant difference was found between the stages and histological types in terms of the serum and BAL fluid VASH-1 concentrations.

Conclusions: BAL VASH-1 concentrations decreased in the lung cancer patients compared to the individuals having a benign lung disease. Considering the results reached in this study, it was thought that the BAL VASH-1 concentrations might be beneficial in distinguishing between the benign and malignant lung diseases.

Keywords: Angiogenesis, Broncoalveolar Lavage Fluid, Lung Cancer, Metastasis, Vasohibin-1.

Akciğer Kanserli Hastalarda Serum ve Bronkoalveolar Lavaj Sıvısında Vasohibin-1 Düzeylerinin Belirlenmesi

ÖZET

Amaç: Akciğer kanseri tüm dünyada kanser olgularının %17'sinden, kanser ölümlerinin ise %23'ünden sorumludur. Vasohibin 1 (VASH-1) endotel hücreleri tarafından sentezlenen bir anjiyogenez inhibe edici faktördür. Bu çalışmada akciğer kanserli hastalarda, bronkoalveolar lavaj (BAL) ve serum VASH-1 düzeylerinin incelenmesi amaçlandı.

Gereç ve Yöntem: Bu çalışmaya toplam 82 hasta katıldı. Bunlardan 39'u benign akciğer hastalığı ve 43'ü malign akciğer kanserine sahipti. Serum ve BAL VASH-1 düzeyleri, enzim bağlı immünosorbent analizi (ELISA) kullanılarak ölçüldü.

Bulgular: Akciğer kanseri grubunda, BAL VASH1 düzeyleri, benign akciğer hastalığı olan gruptan anlamlı derecede düşüktü (p=0,032). Ancak serum VASH-1 düzeyleri açısından her iki grup arasında anlamlı bir fark yoktu (p=0,206). Malign ve benign vakalarda serum VASH-1 ile BAL VASH-1 düzeyleri arasında istatistiksel olarak anlamlı, orta dereceli, pozitif bir korelasyon vardı (benign r= r=0.442, p=0.005; malign r=0.364, p=0.016). Akciğer kanserli hastalar patolojik 'stage' lerine ve histolojik tiplerine göre ayrıldığında, evreler ve histolojik tipler arasında serum ve BAL sıvısı VASH1 konsantrasyonları bakımından anlamlı bir farklılık yoktu.

Sonuç: BAL VASH-1 konsantrasyonları, akciğer kanseri hastalarında benign akciğer hastalığı olan bireylere kıyasla azaldı. Elde edilen sonuçlar ışığında, BAL VASH-1 konsantrasyonlarının benign ve malign akciğer hastalıklarını ayırt etmede faydalı olabileceği düşünülmüştür.

Anahtar Kelimeler: Akciğer Kanseri, Anjiogenez, Bronkoalveolar Lavaj Sıvısı, Metastaz, Vazohibin-1.

INTRODUCTION

Lung cancer constitutes 17% of all cancer cases and accounts for 23% of the deaths caused by cancer all over the world (1). At the time of diagnosis, 86.7% of the cases had locally advanced or advanced stage diseases (2). Although it depends on the stage of the disease, the average 5-year survival rates were found to be 11% between 2000 and 2008 (3). Various genetic and carcinogenic factors have a key role in the etiology. It was reported that the risk for lung cancer increased 24-36 times in the smokers compared to the nonsmokers (4).

The methods used to pathologically diagnose the lung cancer can be applied to the primary tumor and metastasis site. Bronchoscopy is a common method used to diagnose the lung cancer. It has a high diagnostic value especially for the central tumors. On the other hand, the transbronchial needle aspiration and biopsy are widely used in the diagnosis of peripheral lesions (5).

The bronchoscopy, needle aspiration, and biopsy carried out for the diagnostic purposes are expensive and invasive techniques with a high morbidity and they disturb the patient's comfort. Therefore, there is a need for the simple, low-cost, and non-invasive new molecular markers in the diagnosis and follow-up of lung cancer. The purpose of the biochemical studies is to identify the new tumor markers to be used to predict the structural features and prognosis of tumors. VASH-1 is one of the molecules that have been investigated for this purpose.

The VASH-1 is a protein that is composed of a mature protein core of 365 aa, produced at 44 kDa, and known to increase the resistance of endothelial cells to the stress and to stabilize the vessels as well as to terminate the angiogenesis in the terminal region (6,7).

Vasohibin-1 (VASH-1) is a protein that has an anti-angiogenic activity and that is induced by the vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF2), which are some of the angiogenic factors expressed from the activated endothelial cells (8,9). It has been found that the VASH-1 protein expression in the blood vessel endothelial cells of tumors is associated with various cancer types like the breast cancer, hepatocellular carcinoma, non-small-cell lung cancer, prostate cancer, renal cell carcinoma, and the upper urinary tract urothelial carcinoma (10-18).

This study aimed to measure the VASH-1 levels in serum and BAL fluid in the lung cancer patients and to compare the serum and BAL VASH-1 concentrations in the individuals having a benign lung disease. Furthermore, we also examined whether the serum and BAL fluid VASH-1 concentrations were correlated with the lung cancer histological types and the habit of cigarette smoking.

MATERIAL AND METHODS

This study was conducted after receiving the approval from the Ethics Committee of XXX University Faculty of Medicine (20.03.2014, meeting no: 4, decision no: 6). In this study, the 1st group consisted of 43 patients who were admitted to the Chest Diseases Clinic between March 2014 and March 2015 with the complaints such as cough, shortness of breath, and hemoptysis and who were diagnosed with lung cancer by the radiological and biochemical examinations as well as the histopathological evaluation of the samples taken after the bronchoscopy and biopsy (if necessary). The 2nd group consisted of 39 patients who had the same demographic characteristics and diagnosed with non-cancerous lung disease. Of the cases with benign diseases, 7 had been diagnosed with sarcoidosis, 11 tuberculosis, 10 pneumonia, 4 hemoptysis, and 7 chronic obstructive pulmonary disease (COPD). All subjects in the study groups were informed about the study and included in the study after they signed the consent forms.

The inclusion criteria were to be 30-85 years old and newly diagnosed with lung cancer or non-cancer lung disease. The criteria for the presence of non-cancer lung disease were as follows: being admitted with the symptoms suggestive of the lung disease such as cough, shortness of breath, and hemoptysis; and having one of the diseases affecting the interstitial tissue of the lungs such as sarcoidosis, tuberculosis, pneumonia, hemoptysis, and COPD.

The exclusion criteria of the study were as follows: the presence of any malignancy other than the lung cancer; actively getting chemotherapy, immunotherapy, or radiation therapy; and having a surgery for the lungs in the last three months.

Blood Samples: Before starting any medication or carrying out a surgical intervention, the blood samples taken for the routine biochemistry tests were kept in the tube in an upright position for 10-20 min. and then centrifuged at 4000 rpm for 15 min. at +4°C. The serum samples obtained were aliquoted and kept at -80°C until the day of analysis.

Bronchoalveolar Lavage Samples: Before starting any medication or carrying out a surgery and after the bronchoscopy, with the purpose of diagnosing, the brushing was applied to the patients or some serum was administered to a lung segment bronchus which was determined physiologically (provided that biopsy was not carried out). The fluid administered was back-aspirated with a defined pressure. The lavage samples obtained were aliquoted and then kept at -80 °C until the day of analysis.

Methods for the Determination of Analytes: The measurements of the serum and BAL VASH-1 levels were made on the same day to avoid the inter-day variation. The VASH-1 levels in the serum and BAL samples were measured through the

ELISA method using "Human Vasohibin-1 ELISA Kit (Lot:30211832) in line with the instructions of the manufacturer. The values were expressed in ng/mL.

Statistical Evaluation: SPSS v20.0 (Windows, SPSS Inc, IL, US) was used for the statistical evaluations and recording the data. The descriptive statistics of the data obtained were expressed in numbers and % for the categorical variables and in average ± standard deviation for the numerical variables. Kolmogorov Smirnov Test and the histogram graphing method were used for analyzing the data's fitness to the normal distribution. For the data not meeting the normality requirements, Mann-Whitney U test was used to compare two independent groups and Kruskal-Wallis Test was used for the multiple comparisons. Spearman's rho correlation method was used to examine the relationship between the numeric non-normally distributed data. The statistical significance level was set at $p<0.05$.

RESULTS

Information on gender, age and diagnosis of lung cancer type and stage is provided in Table 1. A significant difference was observed between the groups in terms of age (p=0.009). Therefore, in order to determine whether the difference between the cancer patients and the benign patients was due to the age, the weighting was carried out.

Table 1. Clinical characteristics of lung cancer and benign lung disease study populations

Samples	Characteristics	Lung Cancer	Benign lung disease
Total (n)		43	39
Gender (n,%)	Females	7 (16.3%)	17 (43.6%)
	Males	36 (83.7%)	22 (56.4%)
Age (years)	Mean± sd	63.6 ± 10.9	55.6 ± 15.8
Histology (n)	squamous cell carcinoma	20	
	adenocarcinoma	7	
	small cell carcinoma	16	
Stage (n)	II	7	
	III	7	
	IV	29	

The serum VASH-1 levels were below the detection limit in 7 patients in the lung cancer group and in 1 patient in the benign lung disease group. The serum VASH-1 levels in both groups are given in the Table 2. No statistically significant difference was found between the groups in terms of the serum VASH-1 levels (p=0.206) (Figure 1).

Table 2. Serum and BAL fluid VASH-1 Concentrations

Groups	Group 1	Group 2	P
Serum VASH-1 (ng/mL)	0.30±0.25	0.38±0.31	0.206
BAL VASH-1 (ng/mL)	0.10±0.12	0.19±0.18	**0.032**

Values are expressed as mean ± standard deviation

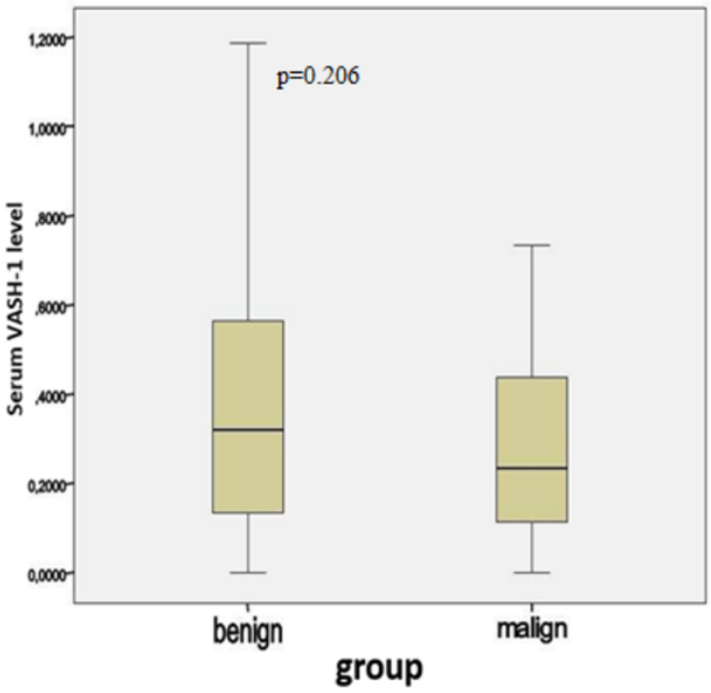

Figure 1. Intergroup comparison of the serum VASH-1 levels

When the BAL fluid VASH-1 levels were evaluated, they were found to be below the detection limit in 8 patients in the lung cancer group and in 5 patients in the benign disease group. The BAL fluid VASH-1 levels in both groups are given in the Table 2. There was a statistically significant difference between the two groups in terms of the BAL fluid VASH-1 results (p=0.032) (Figure 2). There was a highly significant difference in both groups between the means of the BAL VASH-1, which were evaluated separately in the benign and malignant patients after weighting the cases based on the age ($p<0.001$).

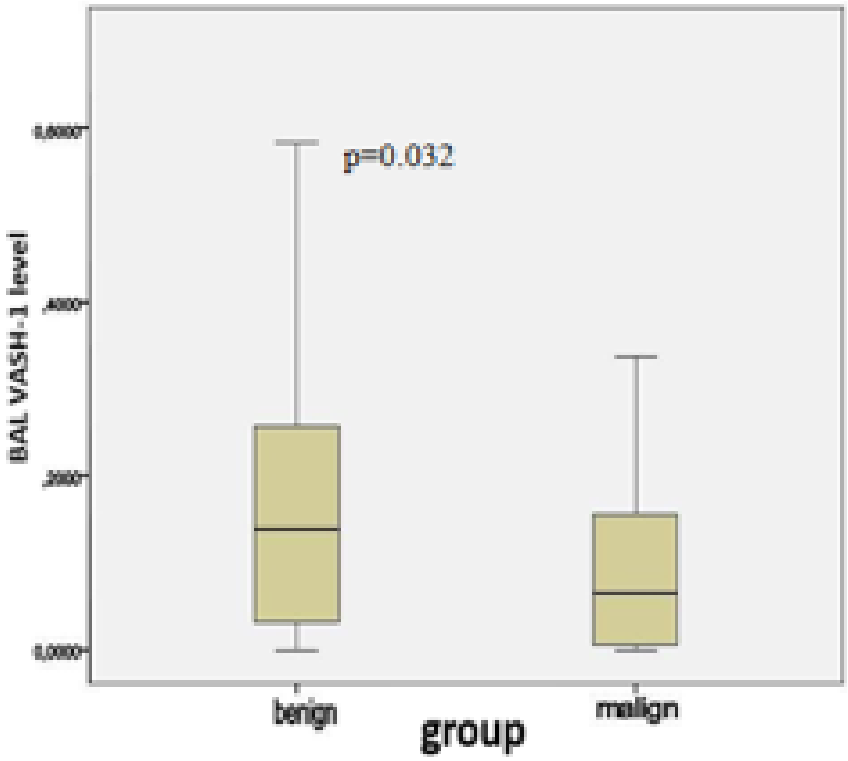

Figure 2. Intergroup comparison of the BAL VASH-1 levels

There was a statistically significantly moderate positive relationship between the serum and BAL fluid VASH-1 levels in the benign and malignant cases (r=0.442, p=0.005 for the benign; r= 0.364, p=0.016 for the malignant).

The lung cancer patients were typed and staged based on the pathology results (Table 1). The result of the comparison of the malignant cases in terms of their stages, the difference between the groups was found to be not significant in terms of the serum (χ^2 = 0.199, p=0.905) and BAL (χ^2 = 1.535, p=0.464) VASH-1 means. Also, no statistically significant difference was observed between the histological types in terms of the serum (χ^2 = 1.608, p=0.448) and BAL (χ^2 = 0.208, p=0.901) VASH-1 means. Even when 27 patients were classified as NSCLC and 16 patients were classified as SCLC, it was observed that there was no significant difference between the groups in terms of the serum (p = 1.000) and BAL (p = 0.308) VASH-1 means.

There was not a significant difference between the serum VASH-1 means of the smokers and the non-smokers (p=0.359). A significant difference was observed between the means of the BAL fluid VASH-1 in the non-smokers and the smokers (p = 0.04). A significant, positive, and high relationship (r=0.365, p=0.002) was found between the serum and BAL VASH-1 levels in the smokers; a significant, positive, and moderate relationship (r=0.571, p=0.026) was also found in the non-smokers. There was a highly significant difference in both groups between the means of the serum and BAL VASH-1, which were evaluated separately in the smokers and non-smokers after weighting the cases based on the age (p<0.001).

In the analysis carried out separately in terms of the means of the serum and BAL fluid VASH-1 between the benign diseases, no significant difference was observed between the benign diseases in terms of the means of the serum VASH-1 (p=0.448) and BAL VASH-1 (p=0.901).

DISCUSSION

Lung cancer is one of the commonest cancers that are highly morbid and mortal. The mortality rate of the lung cancers is high due to the difficulties experienced in early diagnosis, close follow-up, and the right treatment if deemed necessary. On the other hand, the diagnostic value of the noninvasive tests such as cytology and tumor marker in determining the early diagnosis, presence of recurrence, invasion, and metastasis in lung cancer is still not at the desired level. The need for the follow-up at close intervals led the researchers to find the noninvasive biochemical markers instead of the invasive interventions with high morbidity. The promising use of the proteins such as VASH-1, which is a candidate for being a tumor marker, in revealing the presence of tumor, recurrence, invasion, and metastasis paved the way for the researchers to carry out more and more studies on this subject.

As the expression of molecules in the vascular endothelium increases due to various reasons, their levels in the general circulation will also increase. In case the expression of molecules increases in the vascular endothelium in the wall of

lung bronchioles, it is also possible to detect the molecules in the BAL fluid obtained by the washing procedure after the bronchoscopy. Moreover, the contact of the bronchial basal epithelial cells with this fluid can also be a reason for being able to detect these molecules in the BAL fluid. Therefore, the level of some markers in the BAL fluid as well as the serum is examined in the lung cancer cases (19).

The local invasion and metastasis of the tumor cell primarily require the destruction of the basement membrane and the neovascularization. For the neovascularization, various biomolecules stimulating the angiogenesis in the existing vascular endothelial cells need to be synthesized and secreted. VEGF is one of the most important molecules known to activate the angiogenesis (20). With the increase of the synthesis of VEGF, the synthesis of the VASH-1 molecule, which has a key role in the maturation of new vessels and their termination where needed, also increases (8). In various studies carried out on the VASH-1 molecule in recent years, it has been revealed that this molecule is related with the tumor invasion, metastasis, and poor prognosis (21).

In our study, the serum and BAL fluid samples of the individuals with lung cancer and benign lung disease were measured using the ELISA technique and the groups were compared based on these results. Since it was impossible to use the bronchoalveolar lavage samples as well as the serum sample and to take this sample from the healthy individuals, the cancer patients were compared with the patients having a benign lung disease rather than the healthy individuals. While in the lung cancer group, the BAL fluid VASH-1 levels were lower than those having a benign disease; there was no significant difference between the malignant and benign patients in terms of the serum VASH-1 levels. However, a statistically significantly positive correlation was found between the serum and BAL fluid VASH-1 levels in the patients with both benign and malignant disease. The lower VASH-1 levels in the BAL fluid samples of the cancer patients compared to the benign patients explained the fact that the tumor tissue grew faster than the normal tissue and there was more vascular structure which lacked the mural cells and thus was immature.

Furthermore, in the malignant patients, no significant relationship was found between the serum and BAL fluid VASH-1 levels, which were compared based on the classification in terms of the stage and histological type of the tumor. Moreover, the VASH-1 level in the BAL fluid samples in the smokers were found to be lower than that in the non-smokers. These results suggested that the decrease in the VASH-1 levels might be an indicator for the increased cancer susceptibility in the smokers.

In the literature review we carried out, it was found that there were few studies examining the expression of VASH-1 in the tissue samples of the lung cancer patients. In one of these studies, Zhang et al. (16) used the immunohistochemical method to measure the expression of the VASH-1 protein in the biopsy specimens taken from the patients with non-small-cell lung cancer. They detected VASH-1 in the cytoplasm of vascular endothelial cells of both cancer tissue and normal tissue. When the number of samples with high VASH-1 expression was compared with the normal tissue samples, it was found that they were higher in the lung cancer patients. Furthermore, they revealed that the high VASH-1 expression was correlated with the TNM staging, but the high VASH-1 expression in the tissues of the patients with cancer had no significant correlation with the age, gender, smoking, histologic type, and tumor size. The VASH-1 expression was shown to increase as the stage of the disease increased. Also, many studies show that significant correlation between the degree of malignancy (tumor grade and stage) and poor prognosis and VASH1-positive vessel density (18,22,23).

In a study carried out by Watanabe et al. (24) it was found that the preoperative high plasma VASH-1 concentration was related with a better prognosis in the individuals having non-small cell lung carcinoma (24).

In another study carried out on the lung cancer patients, Hosaka et al. (10) examined the lung cancer tissue samples of 44 patients with NSCLC using the immunohistochemical method and inoculated Lewis lung carcinoma (LLC) cells into the VASH1 -/- and wild-type (WT) mice to better explain the function of VASH-1. As a result of the examination carried out on the tissue samples, they showed that the VASH-1 protein was expressed in the tumor stroma more prominently than in the non-cancerous resection sites. In the same study, it was also revealed that as a result of the inoculation of LLC cells into VASH-1 -/- mice, compared to WT mice, the tumor diameter was much larger, its growth was faster, the vascular area was wider, and the vessels were immature and lacked the mural cells. It was also shown that, when the exogenous VASH-1 was administered to the VASH-1 -/- mice, the tumor size in mice was inhibited, the vascular area was reduced, and the tumor vessels become more mature. In conclusion, the study in question suggested that the endogenous VASH-1 protein may be a new test for the diagnosis and treatment of the lung cancer because it inhibited the tumor angiogenesis (10). Our study may be important in terms of the idea that the VASH-1 protein, which is found in low levels in the BAL fluid, can be used for the therapeutic purposes apart from giving information about the tumor density.

CONCLUSION

All in all, the studies have revealed that the VASH-1 protein has a complex inhibitory role in the malignant tumor behavior. It has been asserted in the studies that the low level of VASH-1 can be the indicator for the metastasis, deep invasion, and the poor prognosis. Almost all animal studies in the literature have suggested that the VASH-1 protein is a new treatment modality that can be used to inhibit the angiogenesis in cancer and other diseases. In our study, the VASH-1 level in BAL fluid of the malignant patients was found to be lower than that of the benign patients. This supported the fact that

the angiogenesis was faster and the immature vascular density was higher in the patients with cancer and, therefore, the metastasis and invasion could occur, and the prognosis was worse than the benign patients. Considering the fact found in our study that the VASH-1 levels of BAL fluid were lower in the patients with malignant disease, it was thought that this difference could be used in distinguishing the benign malignant diseases.

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RESEARCH ARTICLE

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The Distribution and The Related Factors of Forward Head Posture Among Medical Students

ABSTRACT

Objective: Forward head posture (FHP) is becoming common in medical students who study for long durations with wrong postures due to intensive curriculum. This study was conducted to determine the frequency of FHP and related factors in medical students.

Methods: The first and second-year medical students filled out the questionnaire including sociodemographic characteristics, activity status, Smartphone Addiction Questionnaire, Beck Depression, Body Awareness, and Perceived Stress Scales after their verbal consent was obtained. FHP and craniovertebral angle values were measured.

Results: 47% of the students had highly severe (≥5 cm), 46.2% had severe FHP (2.5-5 cm), and 6.8% had mild FHP. The mean CVA (Costovertebral Angle) values were determined as 44.31 ± 4.31. The frequency of students whose CVA values are below 45° is 59.3% (140 people). The frequency of highly severe FHP was also found as high in the taller, in males, and in the students with high BMI. In the regression model examining the situations that increase the risk of severe FHP, it was found that depression increased the risk of FHP 2.5 times.

Conclusions: FHP was found to be very common (90%) in medical students. FHP was found to be more severe in students with high depression scores.

Keywords: Forward Head Posture, Medical Student, Beck Depression Scale, Smartphone Addiction Scale.

Tıp Öğrencileri Arasında İleri Kafa Duruşunun Dağılımı Ve İlişkili Olduğu Faktörler

ÖZET

Amaç: İleri kafa duruşu (Forward Head Posture-FHP), yoğun müfredat nedeniyle uzun süre yanlış duruşlarla çalışan tıp öğrencilerinde yaygınlaşıyor. Bu çalışma tıp öğrencilerinde FHP sıklığını ve ilişkili faktörleri belirlemek amacıyla yapılmıştır.

Gereç ve Yöntem: Birinci ve ikinci sınıf tıp öğrencileri, sosyodemografik özellikler, aktivite durumu, Akıllı Telefon Bağımlılığı Anketi, Beck Depresyon, Beden Farkındalığı ve Algılanan Stres Ölçeklerini içeren anketi sözlü onamları alındıktan sonra doldurdu. FHP ve kraniovertebral açı değerleri ölçüldü.

Bulgular: Öğrencilerin %47'sinde çok şiddetli (≥5 cm), %46,2'sinde şiddetli FHP (2,5-5 cm) ve %6,8'inde hafif FHP saptandı. Kraniyovertebral açı (Craniovertebral Angle-CVA) değerleri ortalama 44.31 ± 4.31 olarak tespit edildi. CVA değeri 45°'nin altında olan öğrencilerin oranı %59,3'tür (140 kişi). Uzun boylularda, erkeklerde ve BKİ'si yüksek olan öğrencilerde de oldukça şiddetli FHP sıklığı yüksek bulundu. Şiddetli FHP riskini arttıran durumların incelendiği regresyon modelinde depresyonun FHP riskini 2,5 kat arttırdığı saptanmıştır.

Sonuç: Tıp öğrencilerinde FHP'nin çok yaygın (%90) olduğu saptanmıştır. Depresyon skoru yüksek olan öğrencilerde FHP'nin daha şiddetli olduğu saptanmıştır.

Anahtar Kelimeler: İleri Kafa Duruşu, Tıp Öğrencisi, Beck Depresyon Ölçeği, Akıllı Telefon Bağımlılık Ölçeği.

INTRODUCTION

The rapidly increasing FHP (forward head posture) in modern society is the excessive protrusion of the neck to the anterior of the body (1). The load put on the muscles in the back and neck area increases by 0.45 kg with every 2.5 cm forward positioning of the head that may result in muscle imbalances, posture impairments and FHP which can lead to soft tissue damage, pain in the neck and scapular area, tenderness at associated sites and headaches (2). The prevalence of having FHP in patients with neck pain was found to be 37% in a study (3) suggesting that the correct neck posture is directly related to reducing neck pain. FHP may occur by prolonged use of mobile phones, chairs and beds that do not have good ergonomics, lack of exercise, excessive learning activities and heavy school bags (4). Medical students spend long durations studying at the desk or on the computer due to intensive curriculum which may cause incorrect posture habits without ergonomic conditions.

FHP was found to be higher in people with depression, and a change in posture was observed when depression improved (5). There are studies in the literature that found a relationship between perceived stress, body awareness, depression, head and neck posture, and FHP (6-8). But there is no study examining all these together. Therefore, the aims of this study are; to reveal the prevalence of FHP among medical faculty students, to explore the distribution of FHP; to investigate the relationship between perceived stress, depression, body awareness, head and neck posture.

MATERIAL AND METHODS

This descriptive cross-sectional study which was approved by Sakarya University Faculty of Medicine Ethics Committee (Approval number: 71522473/050.01.04/28) was conducted in 1st and 2nd grades of medical faculty. According to Yeom et al. two methods can be used to detect FHP (1).

There is FHP if the imaginary line between the tragus of the ear and the middle of the shoulder is not on the same line when viewed from the side. And the horizontal length between that two vertical lines indicates the severity of FHP. The level of FHP is classified as slight/severe/highly FHP according to that horizontal length. The slight FHP is accepted as between 1cm-2.5cm, severe FHP between 2.5cm-5cm, and highly severe FHP 5 cm and above (1).

As a second objective method that provides information about FHP is the craniovertebral angle (CVA) which is the angle between the horizontal line passing from the tip of the spinous process of the seventh cervical vertebra and the imaginary line directed from that tip to the tragus of the ear on the same side (9). CVA can be measured by a goniometer or through photographs taken from a side of a person (9,10). There is no cutoff value for CVA but the smaller the CVA, the more severe the FHP grade (3). The average CVA measured in FHP patients is less than 45° (11).

The students also filled a questionnaire asking sociodemographic characteristics, height, body mass index (BMI), weekly average sitting time, standing time, activity status, Beck Depression Scale, Body Awareness Scale, Perceived Stress Scale, and Smartphone Addiction.

Measurements with a goniometer were made by one person and the questionnaires were conducted under observation.

Statistical Analyses: The variables were investigated using analytical methods (Kolmogorov Smirnov test) to determine distribution. Descriptive analysis was defined using means and standard deviations if the variables were normally distributed. Categorical variables were specified as numbers and percentages. Continuous variables were shown as median (25th – 75th) percentiles. Mann Whitney U test was used for comparisons of the not normally distributed data, Student's t test was used in normally distributed data. Logistic regression analysis were used to determine independent predictors of FHP. Hosmer Lemeshow goodness of fit statistics were used to assess model fit. Statistical analyses performed using the SPSS 21.0 software version.

The Evaluation Scales: The Beck depression scale is a self-rating scale consisting of 21 items that evaluate the behaviors in the last week and the risk of depression (12). Categorically, 0-9 points are indicators of minimal depression, 10-16 mild depression, 17-29 moderate depression, 30-63 severe depression. Turkish validity and reliability study has been done (13).

The body awareness scale, developed by Shields et al. in 1989 (14) was asked via the questionnaire having 18 items that scored between 1 and 7 points for each. The higher the score, the better the body sensitivity (14). Turkish validity and reliability have been made for the questionaries (15).

The perceived stress scale, developed by Cohen et al. aims to measure perceived stress in the last month(16). Cronbach Alpha value was found 0.86 in the reliability study (16). Its Turkish validity and reliability study was conducted (17). In the questionnaire, the total score is between 0-32.

Smartphone Addiction Scale: Smartphone Addiction Scale is a Likert-type scale developed by Kwon et al. in 2013 to measure the risk of smartphone addiction in adolescents(18). Total score is between 10 and 60. As the severity of smartphone addiction increases, the score obtained from the scale increases. In the Korean sample, the cut-off score was reported as 31 for men and 33 for women (18). The Turkish validity and reliability study was conducted (19).

RESULTS

In our study, the average age was 20.06 ± 1.33, and 45% of them were male. The incidence of

highly severe FHP in males is higher than in females (p <0.001). The severity of FHP was significantly higher in those with higher BMI and those who were taller (p <0.001; p <0.001, respectively) (Table 1).

Table 1. The distribution of sociodemographic and some personal characteristics (n=242)

Features	FHP (< 5 cm) n (%)	FHP (≥ 5 cm) n (%)	p
Sociodemographic and some personal characteristics			
Gender (n(%))			
Male	41 (32.8)	64 (57.7)	<0.001*
Female	84 (67.2)	47 (42.3)	
Age Median (1.- 3.pc.)	20.0 (19.0-20.5)	20.0 (19.0-21.0)	0.289**
BMI (m2/kg) (1.- 3.pc.)	21.2 (19.7-23.1)	23.4 (20.9-24.8)	<0.001**
Height (m) (1.- 3.pc.)	167.0(161.5-175.0)	175.0 (165.0-181.0)	<0.001**
Chronic disease(n(%))			
Yes	9 (7.3)	12 (11.1)	0.308*
No	115 (92.7)	96 (88.9)	
Activities and physical activity habits			
Average studying duration except school time (Median (1.-3. pc.))	2.00 (1.00-3.00)	2.00 (1.00-3.25)	0.211**
Average sitting time on weekdays (Median (1.-3. pcl))	8.00(6.00-10.00)	7.50(6.00-10.00)	0.459**
Average sitting time over the weekend (Median (1.-3. pc))	8.00(5.00-10.00)	7.00(5.00-10.00)	0.419**
Average time using a computer, mobile phone (Median (1.-3. pc))	4.00 (3.00-5.00)	3.00 (3.00-5.00)	0.094**
Exercising regularly in the last five years			
No exercise	69 (58.5)	57 (52.8)	
Exercise done	44 (37.3)	44 (40.7)	0.389*
Still ongoing	5 (4.2)	7 (6.5)	
Average standing time per day (hours) (Median (1.-3. pc.))	3.00 (2.00-5.00)	3.00 (2.00-4.00)	0.179**
Average continuous head flexion per day (hour) (Median (1.-3. pc.))	3.00 (2.00-5.00)	3.00 (1.13-5.00)	0.798**

*Chi square test **Mann Whitney U Test pc.=percentile

The average standing time of the participants per day is 3.74 ± 2.15 hours. The duration of the students to keep their head in flexion was 3.86 ± 3.38 hours per day. The average sitting time of students on weekdays and weekends is 8.06 ± 2.99, and 7.58 ± 3.50, respectively. The severity of the FHP level of the students does not change according to the time spent sitting, studying, or at the computer. 56% of the students (n=130) have not done any sports in the last five years. No difference was found in terms of head positioning anteriorly according to the weekly sitting time, the time of sitting in front of the computer, the duration of the head flexed continuously, and the average sitting time on weekdays and weekends (Table 1).

Highly severe FHP was detected in 47.0% of the students (n=111), and severe FHP in 46.2% (n=109). The frequency of students whose CVA values are below 45° is 59.3% (n=140).

Exercising status, smoking or not smoking, presence of chronic disease, use of medication, use of the computer in different positions (such as prone or on back, with desk or chair) don't cause a significant difference in gonio distance and CVA (p> 0.005).

49.2% (n=116) of the students had severe depression. It was found that 33.6% (n=75) of the students had smartphone addiction. In most of the students, the smartphone addiction scale score was below the addiction level (Table 2).

Table 2. Distribution of Smartphone Addiction, Beck Depression, Body Awareness, Perceived Stress Scale Scores by FHP

Scales	Total Median (1.-3.pc.)	Slight or severe FHP Median (1.-3.pc.)	Highly severe FHP Median (1.-3.pc.)	p*
Smartphone Addiction	27.0 (21.0-36.0)	28.0 (23.0-37.0)	27.0 (21.0-34.0)	0.504
Beck Depression score	30.0 (26.0-37.0)	29.0 (25.0-36.0)	31.0 (27.0-37.2)	0.172
Body Awareness score	88.0 (76.0-95.0)	87.0 (75.0-94.0)	90.0 (78.0-96.5)	0.063
Perceived Stress Score	14.0 (11.0-18.0)	15.0 (12.0-18.0)	13.0 (10.2-17.0)	0.157

*Mann Whitney U Test FHP=Forward Head Posture pc.=percentile

In the regression model, the dependent variable was categorized as those with a FHP level of 5 cm and above and those with FHP below 5 cm. Beck's depression is categorically classified as (minimal, mild, moderate, severe). Participants were only included in the moderate and severe depression categories. The table shows that the severe depression category increases the risk of having FHP by 2.50 times compared to the moderate depression category. It was detected that the risk of FHP increased 1.17 times with the increase of BMI, 1.04 times with the increase in height, and 1.04 times as the score obtained from the body awareness scale increased (Table 3).

Table 3. Examination of highly severe FHP status through logistic regression in terms of some features

variables	B	S.E	p	Exp (B)	%95 GA	
					Lower	Upper
Height	0.038	0.018	0.034	1.039	1.003	1.077
BMI	0.162	0.058	0.006	1.175	1.049	1.317
Perceived Stress Score	-0.038	0.034	0.264	0.962	0.900	1.029
Smartphone score	0.005	0.016	0.785	1.005	0.973	1.038
Body awareness score	0.026	0.011	0.017	1.027	1.005	1.049
Severe depression*	0.917	0.377	0.015	2.501	1.195	5.235
Having done sports in the last five years	0.138	0.340	0.686	1.147	0.589	2.235
Constant	-12.688	3.490	<0.001	<0.001		

*Severe depression is scored between 30-63 in Beck Depression Scale

DISCUSSION

Kyphosis is seen about twice as often in men than in women, and the risk of the disease is more common, especially in tall men (20). We found in our study that the frequency of highly severe FHP was higher in those who were taller. The median CVA in this study is 45.00, 1.-3. percentile (40.00-47.75). In various studies, the average CVA was found between 45-53 (21). In a study conducted with physiotherapy students, the frequency of FHP was found to be 70%. In the study, the frequency of severe FHP is higher in those with high BMI. In the literature, there are studies in which a negative correlation was found between increased BMI and CVA (10,22).

In this study, the incidence of severe FHP in females was 42.3%, while it was 57.7% in males. FHP was found in 18.18% of the participants in the study of Talati et al.3 Of the subjects participating in our study, 6.8% were found to be slightly FHP, 4.2% as severe FHP, and 47.0% as highly severe FHP. Lee et al.'s study found that those with FHP had narrower CVA and increased flexion in their lower cervical vertebrae (23).

Although there is a difference between the genders in terms of FHP, it is thought that this difference is mostly related to the tallness of the men. Because standing and sitting computer usage times are similar.In the model generated in this study, we detected that those in the severe depression category of the Beck depression scale have an increased risk of having highly severe FHP by 2.50 times. In literature, it has been found that people with usual sadness have more protrusion in the shoulders (24). It also found increased head flexion, thoracic kyphosis, a trend toward left pelvic retroversion in people with major depressive disorder in literature (5).

In the literature, it has been observed that an improvement in head and neck posture is observed with postural awareness and exercise (25). However, in our study, a relationship between regular sports behavior and head and neck posture was not found. This situation is mostly related to the type and frequency of the sport, and instead of asking a specific head and neck exercise, we generally asked about regular exercise behavior.

There is no study examining all these pschological factors and the measurements together. However, there were limitations in our study that prevented the generalization of the study, such as the fact that the study group was medical school students; therefore they had intensive education programs, and most students with moderate and severe depression scores. It has also been found that the stress of medical students creates mental distress which negatively affects their physical health.

CONCLUSION

Approximately 90% of our study group had severe or highly severe FHP which is related to head and neck posture. In the study, FHP was found to be associated with height and depressive mood. Highly severe FHP is quite common in those with severe depression. It has been found that FHP is common in males. In the light of all our results and literature, we can say that FHP awareness should be created among medical students for them to prevent the likely problems they will face associated with head and neck posture disorder in some period of their future life.

This study strongly emphasizes that medical students are at risk for posture disorders. The widespread use of ergonomics awareness, education, and correct application knowledge of ergonomics among the public is necessary for preventing some chronic ergonomic damages such as neck pain and forward head posture.

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RESEARCH ARTICLE

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The Opinions of Family Medicine Residents about Education and Working Conditions in Turkey

ABSTRACT

Objective: In residency education, the educational environment interacts with each component of the training. This study is intended to assess the perceptions of family medicine residents about the educational and working environments from their point of view and to reveal their problems and expectations.

Methods: In this descriptive and cross-sectional study, nationwide 434 family medicine residents' opinions about their educational environment were collected using a survey prepared by the researchers.

Results: The mean age of the residents was 29.26±4.31 years. Women constituted 70.5% (n=306) of participants and 53.7% (n=233) chose family medicine career due to its working conditions. The rate of those who stated that there were no educational family health centers was 57.1% (n=248). More than half (67.5%; n=293) were satisfied with the department that they are getting education. Institutional assessment score (IAS) of those who chose family medicine for working conditions and obligations was lower than the participants who chose it because of their love and interest (p<0.001). The satisfaction score for the residency education (SSRE) was higher for those aged 36 and over than the age group 24-29 (p=0.008) and the age group 30-35 (p=0.005).

Conclusions: Although more than three quarters of the participants stated that activities related to training such as articles and seminar hours were sufficient, approximately one third stated that theoretical and practical education was not sufficient. Another important result was that less than half of the residents believed that when they completed their education, they would be competent to work in all conditions.

Keywords: Family Medicine, Residency, Education Environment, Working Conditions.

Türkiye'deki Aile Hekimliği Uzmanlık Öğrencilerinin Eğitim ve Çalışma Koşulları Hakkındaki Görüşleri

ÖZET

Amaç: Uzmanlık eğitimi sürecinde eğitim ortamı eğitimin her bir bileşeniyle etkileşim içindedir. Bu çalışmanın amacı, Türkiye'deki aile hekimliği uzmanlık öğrencilerinin eğitim ve çalışma ortamlarının kendi bakış açılarıyla değerlendirilmesi, böylelikle sorunlarını ve beklentilerini ortaya koyabilmektir.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel tipte olan bu çalışmada, ülke genelinde 434 aile hekimliği uzmanlık öğrencisinin eğitim ortamları ile ilgili görüşleri, araştırmacılar tarafından hazırlanan anket ile toplanmıştır.

Bulgular: Uzmanlık öğrencilerinin yaş ortalaması 29,26±4,31 yıldı. Katılımcıların %70,5'i (n=306) kadın ve %53,7'si (n=233) aile hekimliğini çalışma şartlarından dolayı seçmişti. Yarısından fazlası (%67,5, n=293) eğitim aldığı alanı seçmekten memnundu. Eğitim aile sağlığı merkezlerinin olmadığını belirtenlerin oranı %57,1'di (n=248). Çalışma şartlarından ve zorunluluklardan dolayı aile hekimliğini seçenlerin kurum değerlendirme puanı (KDP) sevgisi ve ilgisinden dolayı seçen katılımcılardan düşüktü (p<0,001). Uzmanlık eğitiminden memnuniyet puanı (UEMTP) 36 yaş ve üzerindekilerin, 24-29 yaş (p=0,008) ve 30-35 yaş grubuna (p=0,005) göre yüksekti.

Sonuç: Katılımcıların dörtte üçünden fazlası makale, seminer saatleri gibi eğitimle ilgili faaliyetlerin yeterli olduğunu belirtmesine rağmen yaklaşık üçte birinin teorik ve pratik eğitimin yeterli olmadığını belirtti. Diğer bir önemli sonuç da uzmanlık öğrencilerinin yarısından azının eğitimlerini tamamladıklarında her koşulda çalışabilecek yeterlilikte olacaklarına inanmalarıydı.

Anahtar Kelimeler: Aile Hekimliği, Uzmanlık Eğitimi, Eğitim Ortamı, Çalışma Koşulları.

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INTRODUCTION

Family Medicine residency education aims to provide the residents with clinical knowledge, skills, attitudes and behaviors in line with the basic principles included in the definition of family medicine, as well as providing appropriate opportunities for the development of researcher and management qualifications and health education skills (1). There are lots of studies in Turkey in recent years as in the whole world which state that residency education should be a process structured within the framework of certain standards, medical dignity and ethical principles, and it should shaped in line with the expectations of society and certified by objective-based testing and assessment (1,2,3).

In the medical education discourse, the 'environment' or 'educational environment' is increasingly emphasized. In residency education, the educational environment interacts with each component of the education and how the educational environment is perceived by the trained ones plays a key role in determining the quality of learning processes (4).

The "International Standards of Medical Education" reports published by the World Federation for Medical Education (WFME) following the study in 1998 to determine international standards for medical education, called "Triology" later, are collected under three headings. One of these titles is postgraduate medical education (WFME). With these standards, it is aimed to provide a method for quality improvement in medical education to be applied in programs at all stages of medical education and in institutions responsible for medical education. WFME highlights the educational environment as one of the basic standards in the evaluation of postgraduate medical education programs collected under nine main headings (2).

Various elements related to the academic and social environment in educational institutions can create different effects from individual to individual at various levels both in the curriculum and in the education process, that is, the educational environment can affect the motivation of the student in a positive or negative way (4). The dimensions of the educational environment in medicine, such as the number of students and educators, their qualifications, the size of the library, laboratory, infrastructure and other resources, the number of publications, research, training program documents, and learning objectives are known, but there are very few publications on how they are evaluated by those who are trained (5).

The quality of residency training programs can be assessed with the educational environment. The assessment of the educational environment provides more accurate information about the content of the education and the institutional culture and leads to an increase in the quality of the education of the institutions and therefore the graduates, and an increase in the belonging to the institution (6). Actually, the Medical Specialization Board Curriculum Development and Standards-Setting Committee define the educational environments in detail and emphasize the importance of the subject (1).

This study mainly aims to determine the educational and working environments of family medicine residents in Turkey from their point of views. Secondly, depending on the results about their problems and expectations contributing to the development of residency education was aimed.

MATERIAL AND METHODS

Study Population: The population of this descriptive and cross-sectional study consists of family medicine residents who use social media and receive full time education at private and public university and education and research hospitals. In the calculation made by looking at the cadres of the universities at the time of the research, approximately 790 residents were studying at universities, and approximately 870 residents were studying at medical faculties and training and research hospitals of Ministry of Health. The sample size which was 377 was calculated with a 5% margin of error and 95% confidence interval. However, considering that there may be questionnaires left blank or incompletely filled, it was aimed to reach approximately 400 family medicine residents with an increase of 5%. Sampling was reached announcing family medicine residents in Turkey through different social networks during nine months and asking the volunteers to fill in the survey in the given link explaining the purpose of the study.

Data Collection: A survey consisting of two parts was used. The first part, the socio-demographic information form, consists of 14 questions. In the content of the form, the institution to which the participant is affiliated, nationality, age, gender, marital status, having a child, economic status, medical school he graduated from, the rank of his specialty training in TUS, the time spent in specialization training, the reason for choosing the field of specialization training. There are questions about the state of being satisfied with the choice, the state of being satisfied with the city where he lives, and the state of wanting to choose the same field of specialization if he has the chance to choose again".

The second part is the information form with two sections, consisting of education and working environment, inspired by the survey questions prepared for another study approved by the ethics committee of Meram Faculty of Medicine, WFME main topics, Medical Specialization Board Curriculum Development and Standards-Setting Committee recommendations and similar studies. (1,2,3,4,5,7,8,9,15,16,17,18). It was created in a structure that was evaluated with a five-point Likert (1- Never 2- Very rarely 3-Sometimes 4- Often 5-

Always) consisting of 25 statements under two headings. The first part consists of questions about the education and working conditions in the department where specialization is received, and the second part in general in the hospital where she works.

Questions to evaluate the department; working order, the process and requirements of education, educational activities such as article and seminar hours, the adequacy of theoretical and practical education, thesis consultancy and publication process, scientific activities, the existence of the education family health center (e-ASM), the evaluation methods of the specialty student, the educational environment, consists of questions to measure interpersonal relationships.

Questions asked to evaluate the institution; information facilities such as the internet and computers, research opportunities such as scientific research projects (BAP), scholarships, administrative services such as human resources, secretarial services, social opportunities such as theatre, cinema, concert, sports etc., physical working environments such as polyclinics, services, libraries, laboratories. It consists of questions aimed at measuring resting environments such as assistant rooms and the satisfaction of the institution in general.

A total scale score was obtained for both 25-item subsections (25-125 points) and 50 statements in total (50-250 points), and there were no reverse scored questions

Statistical Analysis: While evaluating the obtained results, SPSS (Statistical Package for Social Sciences for Windows) 22.0 program was used for statistical analysis. Descriptive statistics of continuous variables were indicated with mean and standard deviation, and descriptive statistics of categorical data were stated as frequency and percentage. In comparison of quantitative data, Independent Samples-T test was used in paired groups for those meeting the normal distribution assumption, and One-Way Analysis of Variance (One-Way ANOVA) was used in multiple groups. Mann-Whitney U test and Kruskal Wallis test were used for those who did not meet the normal distribution assumption. In case of difference between groups, the significance was evaluated with Post-Hoc Tukey and non-parametric Post-Hoc (Tamhane's T2) tests. Statistically, a value of $p < 0.05$ was considered significant.

RESULTS

The mean age of the participants was 29.26 ± 4.31 (minimum: 24, maximum: 51) years and 70.5% (n=306) of them were women.

In Examination for Specialty in Medicine (TUS) of the field where they received residency education, the answer of 66.4% (n=288) of the residents to the question about the order of preference was the first three. 53.7% (n=233) of the residents participating in the study chose family medicine for working conditions and 21.6% (n=94) of them chose it because of their love and interest.

The internal consistency coefficient of the questions for the department of specialization was calculated as crα=0.940. The internal consistency coefficient of the questions about the institution where the specialist training was received was calculated as crα=0.952.

Generally, residents were satisfied 67.5% (n=293) with their selection of family medicine. The rate of those who stated that they would like to choose family medicine again if they had a second chance was 64.0% (n=278). Socio-demographic characteristics of the participants are shown in Table 1.

The answer of 30.2% (n=131) never/very rarely to the item "Theoretical education is sufficient" and 30.6% (n=133) also answered never/very rarely to the item "Applied education is sufficient according to standards". The rate of those who answered never/very rarely to the item "We have an Educational Family Health Center" was 57.1% (n=248).

In this study, 36.9% (n=160) answered never/very rarely to the item "Physical work environments (outpatient clinic, service, etc.) are sufficient" and 56.5% (n=245) also responded never/very rarely to item "Resting environments (assistant-duty room, etc.) are sufficient." The 44.5 percent (n=193) answered as" most of the time and always" to the item "I believe that I will have the competence to work in any condition when I complete the residency education."

In this study, there was no statistically significant difference between their department assessment scores (DAS) and their gender (p=0.255) and the time spent in residency education (p=0.173).

When the DAS and the order of preference for the field of residency education in TUS were compared, a statistically significant difference was found (p=0.008) between the DAS of the participants (91.68±16.77) who preferred in the top three and the DAS of those who preferred in the fourth place and after (85.78±19.17).

Average DAS of the participants (a) who responded to the question "Why did you choose the field where you received residency education?" as " working conditions" was 88.31±17.21, DAS of those who said obligation (b) was 80.38±16.85, DAS of those who said career and academic development (c) was 89.00±24,71, for those who said love and care (d) it was 95.94±16.63 and for those who responded as for the benefit of society (e), it was 94,89±15,86. A significant difference was found between a and d (p=0.006), b and d (p<0.001) and b and e (p=0.002).

In the study, the average institution assessment scores (IAS) was found to be 77.27±20.02 in men and 71.64±19.09 in women, and there was a significant difference between genders (p=0.006).

No statistically significant difference was found between the participants' order of preference for the field of residency education (p=0.062) and the time spent in the residency education (p=0.320) and their IAS. The average department assessment and institution assessment scores of the participants according to the socio-demographic data are shown in Table 1.

When the age groups and the total satisfaction score for the residency education (SSRE) were compared, the score of the age group 36 and over was significantly higher than the score of the age group 24-29 (p=0.008) and the age group 30-35 (p=0.005). The mean SSRE was 168.35±35.66 in men and 160.58±32.72 in women, and there was a significant difference between genders (p=0.029). The total average satisfaction score for the residency education of the participants according to socio-demographic data are shown in Table 2.

Table 1. The average department and institution assessment scores according to the sociodemographic data of the participants

		n(%)	DAS	p	IAS	p
The institution	The Ministry of Health	297(68.4)	89.31±17.75	0.654	72.36±19.55	0.143
	The University	137 (31.6)	90.13±17.94		75.32±19.35	
Age	24-29 group	298 (68.7)	89.40±16.18	**0.047** [a]	72.85±18.38	**0.010**[a,b]
	30-35 group	102 (23.5)	87.27±20.94	**0.023** [b]	71.41±22.34	
	36 age and over group	34 (7.8)	98.00±19.14		82.94±17.87	
Gender	Male	128 (29.5)	91.08±19.06	0.255	77.27±20.02	**0.006**[c]
	Female	306 (70.5)	88.94±17.23		71.64±19.09	
Economic status	Good	118 (27.2)	87.63±20.04	**0.045**	75.62±21.07	**0.017**[d]
	Moderate	287 (68.4)	90.82±16.65		73.10±18.74	**0.049**[e]
	Worse	19 (4.4)	82.10±18.33		61.94±18.01	
The place of family medicine in the preference list in TUS[*]	First three place	288 (66.4)	91.68±16.77	**0.008**[f]	74.63±20.02	0.062
	Fourth place and beyond	132(30.4)	85.78±19.17		70.00±18.44	
	Those who don't remember or leave blank	14 (3.2)	82.07±18.81		76.78±15.54	
The time spent in residency	0-12 month	152 (35.0)	90.29±16.50	0.173	74.94±18.80	0.320
	13-24 month	127 (29.3)	91.26±18.45		73.43±20.54	
	25 month and over	155 (35.7)	87.49±18.36		71.58±19.32	
The reasons of selecting family medicine in residency	Working conditions	233 (53.7)	88.31±17.21	**0.006**[g] **<0.001**[h] **0.002**[ı]	71.10±18.73	**0.001**[g] **<0.001**[h]
	Obligation	52 (12.0)	80.38±16.85		66.78±17.14	
	Career and academic development	8 (1.8)	89.00±24.71		65.62±29.99	
	Love and interest	94 (21.6)	95.94±16.63		80.74±19.32	
	Work for the benefit of society	37 (8.5)	94.89±15.86		77.81±17.58	
	Economic reasons	5 (1.2)	91.20±29.76		75.20±24.76	
	Recommendation of somebody	5 (1.2)	84.40±19.45		80.40±31.25	
Satisfaction with the selection of family medicine in residency	Satisfied / very satisfied	293 (67.5)	93.95±16.47	**0.034**[j] **<0.001**[k,l]	77.38±19.36	**<0.001**[k,l]
	Indecisive	116 (26.7)	82.11±16.23		66.05±17.09	
	Not at all satisfied / not satisfied	25 (5.8)	72.96±18.95		59.12±15.62	
Satisfaction with the city where they live	Satisfied / very satisfied	317 (73.0)	92.20±16.34	**<0.001**[l] **0.001**[k]	75.84±19.00	**<0.001**[l] **0.007**[k]
	Indecisive	69 (15.9)	83.62±19.56		68.17±17.83	
	Not at all satisfied / not satisfied	48 (11.1)	80.81±19.81		63.90±21.19	
Selecting the same specialty (family medicine) if given a chance of selection again	High probable/Absolutely yes	278 (64.0)	93.62±16.38	**0.001**[m] **<0.001**[n,o]	77.25±18.96	**0.001**[m] **<0.001**[n] **0.004**[o]
	Not sure	104 (24.0)	86.42±17.66		69.63±18.47	
	Never/Probably	52 (12.0)	74.25±15.87		59.54±16.88	

[*]**TUS=** The National Exam for Specialty in Medicine
DAS: Department Assesment Scores
IAS: Institution Assessment Scores
a:Statistical significance between 24-29 group-36 age and over group **b:**Statistical significance between 30-35 group-36 age and over group **c:**Statistical significance between male-female **d:**Statistical significance between good-worse **e:** Statistical significance between modarete-worse **f:**Statistical significance between first three place-fourth place and beyond **g:**Statistical significance between working conditions-love and interest **h:**Statistical significance between obligation-love interest **ı:**Statistical significance between obligation-work for the benefit of society **j:**Statistical significance between indecisive-not at all satisfied/not satisfied **k:** Statistical significance between satisfied /very satisfied-indecisive **l:**Statistical significance between satisfied /very satisfied- not at all satisfied/not satisfied **m:**Statistical significance between high probable/Absolutely yes-not sure **n:**Statistical significance between high probable/absolutely yes-never/probably **o** Statistical significance between not sure- never/probably

Table 2. The satisfaction score for the residency education according to socio-demographic data of the participants

		n(%)	SSRE	p
The institution	The Ministry of Health	297(68.4)	161.68±33.42	0.279
	The University	137 (31.6)	165.00±34.45	
Age	24-29 group (a)	298 (68.7)	162.24±31.39	**0.008[a]** **0.005[b]**
	30-35 group (b)	102 (23.5)	158.68±38.90	
	36 age and over group (c)	34 (7.8)	162.87±33.76	
Gender	Male	128 (29.5)	168.35±35.66	**0.029[c]**
	Female	306 (70.5)	160.58±32.72	
Economic status	Good (a)	118 (27.2)	163.26±38.30	**0.045**
	Moderate (b)	287 (68.4)	163.92±31.64	
	Worse (c)	19 (4.4)	144.05±32.01	
The place of family medicine in the preference list in TUS*	First three place(a)	288 (66.4)	166.31±33.39	**0.010[d]**
	Fourth place and beyond (b)	132(30.4)	155.78±34.10	
	Those who don't remember or leave blank (c)	14 (3.2)	158.85±28.91	
The time spent in residency	0-12 month	152 (35.0)	165.23±32.01	0.215
	13-24 month	127 (29.3)	164.69±36.32	
	25 month and over	155 (35.7)	159.07±33.14	
The reasons of selecting family medicine in residency	Working conditions (a)	233 (53.7)	159.41±32.44	**0.001[e]** **<0.001[f]** **0.004[g]**
	Obligation (b)	52 (12.0)	147.17±30.37	
	Career and academic development (c)	8 (1.8)	154.62±49.91	
	Love and interest (d)	94 (21.6)	176.68±32.60	
	Work for the benefit of society (e)	37 (8.5)	172.70±30.17	
	Economic reasons (f)	5 (1.2)	166.40±51.07	
	Recommendation of somebody (g)	5 (1.2)	164.80±35.73	
Satisfaction with the selection of family medicine in residency	Satisfied / very satisfied (a)	293 (67.5)	171.32±32.23	**<0.001[h,ı]**
	Indecisive (b)	116 (26.7)	148.16±28.82	
	Not at all satisfied / not satisfied (c)	25 (5.8)	132.08±32.16	
Satisfaction with the city where they live	Satisfied / very satisfied (a)	317 (73.0)	168.03±31.59	**0.001[h]** **<0.001[ı]**
	Indecisive (b)	69 (15.9)	151.79±33.48	
	Not at all satisfied / not satisfied (c)	48 (11.1)	144.70±38.35	
Selecting the same specialty (family medicine) if given a chance of selection again	High probable/Absolutely yes (a)	278 (64.0)	170.86±31.76	**<0.001[j,k,l]**
	Not sure (b)	104 (24.0)	156.04±32.46	
	Never/Probably (c)	52 (12.0)	133.78±27.60	

*__TUS=__ The National Exam for Specialty in Medicine

SSRE: Satisfaction Score for the Residency Education

a:Statistical significance between 24-29 group-36 age and over group **b:**Statistical significance between 30-35 group-36 age and over group **c:**Statistical significance between male-female **d:**Statistical significance between first three place-fourth place and beyond **e:**Statistical significance between working conditions-love and interest **f:**Statistical significance between obligation-love interest **g:**Statistical significance between obligation-work for the benefit of society **h:** Statistical significance between satisfied /very satisfied- indecisive **ı:**Statistical significance between satisfied /very satisfied- not at all satisfied/not satisfied **j:**Statistical significance between high probable/Absolutely yes-not sure **k:**Statistical significance between high probable/absolutely yes-never/probably **l:** Statistical significance between not sure-never/probably

DISCUSSION

In general, there are studies to measure the difficulties in all branches experienced by residents in their education and working conditions. Unlike other specialties, there are limited numbers of studies evaluating the education and working conditions of family medicine residents who will work in primary health care. Due to the limited number of studies on this subject in medicine, we believe that it has made significant contributions in terms of its results, due diligence and the creation of medical education curriculum.

The participants of the study were generally (70.5%) women. Similar studies also show that more than half of the participants are women (7, 8, 9). It was determined that 50.6% of the family medicine residency consists of female physicians. As a matter of fact, this is regarded as an expected situation considering the trend in family medicine education consisting of women at the rate of 60% since 2004 (10). A study conducted in Canada shows that the weekly working hours of female doctors are less than male doctors, and that they take a day off for family reasons more than male doctors (11). The reason why women prefer it more may result from the fact that women see it as a field where they can minimize the conflict between family duties and job responsibilities because there aren't heavy working conditions during the period of residency and working in the field later.

In a study dealing with the factors that affect the choice of family medicine residency education, it was observed that the students who did not plan an academic career mostly preferred family medicine residency (12). Similarly in another study, only 26% of the residents who want to choose the family medicine see it as the profession of the future (13). Karaoğlu et al. point out that 62.1% of family physicians do not expect an increase in their career (14). Actually, regarding the reason for choosing the field of residency education, 1.8% of the participants

in this study gave answers about career and academic development such as self-improvement, the branch of the future, academic staff shortage and the desire to become an academician. The reason for this low rate may be the low expectations of residents from the future of the family medicine specialty.

Approximately two-thirds of the participants in this study stated that they were satisfied with being a family medicine resident. Yıldırım et al. also found out that 87.50% of the participants were satisfied with being family medicine residents (9). In Canada, in 2012, 317 family medicine residents in their first year were examined and it was determined that 92% of them were satisfied with choosing family medicine (15). As it is stated by the participants, the reason for their satisfaction could be because they see it as the most appropriate field for them clinically and socially, because it is their ideal and they like it and do it willingly and they don't have too many extra shifts depending on the family medicine discipline.

In a study in Saudi Arabia in regard to the perceptions of training, only 12 (9.1%) residents believed that the teachers were model teachers, while 52 (39.4%) residents believed that the teachers need retraining (7). According to the results of the "Residency Training Workshop Report in Medical Departments" published by the Council of Higher Education (CoHE) in 2017, similar to this study, 13% the participants stated that there is no routine training program (16). Similarly in this study, 12-14% of the residents stated that their educational processes and training requirements were not defined. Considering the historical process, while the primary problem in education in the early 2000s was the lack of training programs and standards, the decrease in the emphasis on the lack of training programs and standards (from 39% to 12%) in the last years and till this study shows that the standards and educational programs are established in many institutions.

According to a previous study in Turkey more than three quarters of 1069 residents stated that there were regular training sessions in their departments; about two-thirds stated that theoretical education was insufficient, and one-third stated that applied education was also insufficient (17). Similarly, in this study, more than three quarters of the residents stated that educational activities such as articles and seminar hours were carried out regularly and approximately one third of them stated that theoretical and applied education was insufficient. Although this study is the most detailed study, it should be supported by other qualitative and quantitative studies on this subject.

More than half of the participants of this study said they didn't agree with the statement "we have an educational FHC". When we look at the literature, it is seen in various studies that there is a rotation need for the educational family health center planned for education in primary health care during family medicine residency (7,8,18). It is seen that the rate of the participants who had field training in educational family health centers is 36% (9). Although family medicine residency is essentially a primary care residency, it suggests that adequate time is not given to primary care education in the current family medicine residency curriculum. Therefore, there is a need for a training center for residents (19).

A study in Japan involving 1.124 assistant physicians found that participation in scientific activities was associated with their overall satisfaction with residency education. The assistants who did not participate in scientific activities stated that they did not have time and interest and there was a lack of consultants and training (20). Encouraging and supporting participation in scientific activities such as research and planning contributes to learning (17,20). This study showed that more than half of the participants" research activities were supported and thesis advisory was sufficient. However, about one third had scientific publications other than their thesis. The reason for this may be the lack of education and motivation regarding the planning and using a scientific research, as well as the lack of interest and time of residents.

Yıldırım et al. point out that nearly half (49.50%) of family medicine residents believe that they received a good education (9). Similarly, in this study, approximately half of the participants (44.50%) stated that they believe that they will have the competence to work in any condition when they complete their residency education. The reason why nearly one out of every two physicians does not feel qualified to work under all conditions may result from the constantly changing policies of the country, the lack of experience, and the education they have received in a tertiary hospital rather than in a primary care.

The department assessment score, institution assessment score and the total satisfaction score for the residency education of this study participants aged 36 and over were higher than the participants in the age groups 24-29 and 30-35. Considering the literature, although there are studies (21,22) with no relationship between age and job satisfaction, there are also studies showing that there is a relationship between age and job satisfaction (23,24). Depending on the increase in professional experience in later years, there is an increase in job satisfaction and residency education satisfaction.

In a systematic literature review, it is noteworthy that physicians who choose family medicine fondly and willingly, who think that it is suitable for their personal values and who aim to benefit the society, have a high satisfaction with family medicine (25,26). Similarly, in this study, when the resident physicians were asked the reasons for choosing their residency education, the department assessment score and total satisfaction score for the residency education of the participants

who stated that they chose it because of their love and interest were higher than the scores of those who chose it for the working conditions and obligations. The fact that residents choose their residency according to their skills and interests rather than working conditions and obligations may enable them to adopt their work and thus increase their job and education satisfaction.

Limitations of the study: This study could not be done face to face due to the pandemic. The items were designed depending on literature because of the lack of a validated questionnaire.

CONCLUSION

Although family medicine residents chose these departments willingly, it is seen that they are experiencing dissatisfaction due to some deficiencies in the residency education and insufficient physical conditions. In the most important era of a caring and devoted profession, it is important for the future of medicine to improve and support the residency training of the residents. In our country, as well as all over the world, there is an effort to establish education curriculum in accordance with the standards determined by WFME such as education program, students, academic staff, educational environment, assessment and evaluation. However, there is limited number of studies examining whether these standards are applied in the field of family medicine. In this study, it was tried to evaluate the education and working conditions in the department and the institution with the questions prepared based on the previous studies in the literature and the standards of the WFME. For this reason, it can be thought that the results of this study will be a guide in evaluating the situation in education and working conditions in new studies. The total internal consistency coefficient of the questions in the department of residency education and the institution was found to be high and it was accepted as reliable. We think that detailed studies should be done to develop scale on this subject.

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RESEARCH ARTICLE

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Decreased Oxidative Stress Markers in Patients with Active and Generalized Vitiligo

ABSTRACT

Objective: Oxidative stress has been shown to play a role in the pathophysiology of several diseases, making it a popular yet contentious research area. There is some evidence that selective melanocyte destruction may have developed in vitiligo patients as a result of elevated oxidative stress. The purpose of this study is to investigate the impact of oxidative stress on lipid, protein, and nucleic acid metabolism in vitiligo patients.

Methods: We used ELISA method to measure serum oxidative stress markers in patients with generalized vitiligo who had newly formed lesions in the previous three months but had not been treated, as well as healthy controls. Malondialdehyde (MDA), 2,4-dinitrophenyl hydrazone (DNPH), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and uncoupling protein 2 (UCP2) levels were measured to assess the influence of reactive oxygen derivatives on lipid, protein, nucleic acid metabolism, and mitochondria, respectively.

Results: The study included 84 participants, including 64 active generalized vitiligo patients and 20 healthy controls with similar age and gender distribution. In the serum of vitiligo patients, we detected significantly lower levels of MDA (ng/mL, mean±SD=12±19; 33.4±35.9), DNPH (ng/mL, mean±SD=2±3.1; 6±7.4), 8-OHdG (ng/mL, mean±SD=11.7±17.9; 32.7±37) and UCP2 (ng/mL, mean±SD=8.7±13.7; 21.5±28.4.

Conclusions: Although there is significant evidence that oxidative stress plays a role in the pathophysiology of vitiligo, the studies should be interpreted cautiously due to the heterogeneity in the methodology, complexity of the oxidative stress pathways, and potential publication bias. Large-scale studies using a standardized methodology are required to determine how significant oxidative stress is in the core pathophysiology of vitiligo and which pathways it primarily affects.

Keywords: Deoxyguanosine, Malondialdehyde, Uncoupling Protein 2, Vitiligo.

Aktif ve Generalize Vitiligolu Hastalarda Azalmış Oksidatif Stres Belirteçleri

ÖZET

Amaç: Oksidatif stresin, birçok hastalığın patofizyolojisinde rol oynadığı gösterilmiş ve bu da onu popüler ancak tartışmalı bir araştırma alanı haline getirmiştir. Vitiligo hastalarında, artmış oksidatif stres sonucu seçici melanosit hasarının gelişmiş olabileceği yönünde bazı kanıtlar vardır. Bu çalışmanın amacı, vitiligo hastalarında oksidatif stresin lipid, protein ve nükleik asit metabolizması üzerindeki etkisini araştırmaktır.

Gereç ve Yöntem: Son üç ayda yeni oluşan lezyonları olan ancak tedavi edilmemiş generalize vitiligolu hastalarda ve sağlıklı kontrollerde, serum oksidatif stres belirteçlerini ölçmek için ELISA metodunu kullandık. Reaktif oksijen türevlerinin lipid, protein, nükleik asit metabolizması ve mitokondri üzerindeki etkisini incelemek için sırasıyla malondialdehit (MDA), 2,4-dinitrofenil hidrazon (DNPH), 8-hidroksi-2'-deoksiguanozin (8-OHdG) ve ayırıcı protein 2 (UCP2) seviyeleri ölçüldü.

Bulgular: Çalışmaya 64 aktif generalize vitiligo hastası ve benzer yaş ve cinsiyet dağılımına sahip 20 sağlıklı kontrol olmak üzere toplam 84 katılımcı dahil edildi. Vitiligo hastalarının serumunda sağlıklı kontrollere göre anlamlı olarak azalmış MDA (ng/mL, ortalama±SS=12±19; 33.4±35.9), DNPH (ng/mL, ortalama±SS=2±3.1; 6±7.4), 8-OHdG (ng/mL, ortalama±SS=11.7±17.9; 32.7±37) ve UCP2 (ng/mL, ortalama±SS=8.7±13.7; 21.5±28.4) seviyeleri tespit edildi.

Sonuç: Oksidatif stresin vitiligo patofizyolojisinde rol oynadığına dair önemli kanıtlar olmasına rağmen, metodolojideki heterojenlik, oksidatif stres yolaklarının karmaşıklığı ve olası yayın yanlılığı açısından çalışmalar dikkatli bir şekilde yorumlanmalıdır. Vitiligonun merkezi patofizyolojisinde oksidatif stresin ne kadar önemli olduğunu ve öncelikle hangi yolakları etkilediğini belirlemek için standart bir metodoloji kullanan büyük ölçekli çalışmalar gereklidir.

Anahtar Kelimeler: Deoksiguanozin, Malondialdehit, Ayırıcı Protein 2,Vitiligo.

INTRODUCTION

Vitiligo is a chronic, acquired pigmentation disorder characterized by the selective loss of epidermal melanocytes, resulting in depigmented patches on the skin (1,2). The precise mechanisms that cause melanocyte destruction are not completely understood. The oxidant-antioxidant theory proposes that an increase in reactive oxygen species (ROS) and/or a decrease in antioxidants may trigger melanocyte death, initiating or aggravating the disease (3–5).

Reactive oxygen species are produced from oxygen as a result of metabolic activity in cells, such as mitochondrial respiration or melanogenesis (2,6,7). They serve as signal molecules but can injure the cell at high concentrations (6). To counteract the detrimental effects of ROS, a variety of antioxidant defense mechanisms are available (8,9). Increased ROS and decreased antioxidants disrupt this balance, causing oxidative stress and resulting in non-specific damage to proteins, lipids, and nucleic acids (10–13). Oxidative stress has been intensively researched in recent decades and has been associated with a number of diseases, including vitiligo (10,13–17). However, a major issue is that study designs and outcomes are often varied, making generalization difficult (10,16).

ROS are difficult to quantify since they are short-lived and labile; hence, stable byproducts are measured instead (18,19). Although ROS have no specific target (18), their primary focus may shift depending on the pathophysiology of the disease, and markers should be used accordingly (15). Although an increase in total oxidants and a decrease in total antioxidants have been observed in the serum of vitiligo patients (2), the data is ambiguous as to which pathways are targeted the most during oxidative stress.

The current study was designed to investigate the impact of oxidative stress on lipid, protein, and DNA metabolism in vitiligo patients. To examine lipid metabolism, we assessed malondialdehyde (MDA) levels, an endproduct of polyunsaturated fatty acid peroxidation (17). 2,4-dinitrophenyl hydrazone (DNPH) (15,20) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) (12,21) levels were measured to assess protein and DNA oxidation, respectively. We also measured uncoupling protein 2 (UCP2) levels, a protein found in the inner membrane of mitochondria that increases in response to oxidative stress in order to reduce ROS formation (11,22).

MATERIAL AND METHODS

All procedures involving human participants were in accordance with the Helsinki Declaration. The study protocol was approved by the Duzce University Health Research Ethics Committee (08/2018). All subjects provided written informed consent prior to enrollment.

Subjects: Patients were recruited from Duzce University's dermatology outpatient clinics. The study included 64 patients with generalized vitiligo aged 10–65 years old who had newly formed depigmented pathes in the previous three months but had not received any topical or systemic treatment. The control group consisted of 20 healthy people who were chosen to be similar to the patient group in age and gender. The study excluded participants who had diabetes, thyroid disease, infectious diseases, autoimmune diseases, or malignancy.

Blood Sampling & Analysis: The participants' venous blood samples were obtained in the morning under sterile settings after they had fasted for 12 to 14 hours overnight. After centrifuging the samples at 3000 rpm for 10 minutes, the sera was separated and stored at -80°C until the ELISA was performed. MDA, DNPH, 8-OHdG, and UCP2 levels were determined using a GenX microELISA device.

To perform an ELISA, serum samples were first treated with enzymes coated with monoclonal antibodies. After that, samples were incubated with biotin-labeled antibodies, and finally streptavidin-HRP was added to form immune complexes. The samples were washed to remove unbound enzyme before being treated with chromogen solutions A and B, which turned the samples blue and yellow, respectively. The concentration of markers was then determined using color chromatography (23).

Statistical Analysis: The statistical analysis software SPSS (version 26.0; SPSS Inc., Chicago, IL, USA) was used to analyze the data. The mean and standard deviation were used to Express descriptive statistics for continuous variables. The Shapiro-Wilk test was used to examine the distribution of the data. The Mann-Whitney U test was used to compare continuous and non-normally distributed data in independent groups. The median, interquartile range, mean, and standard deviation were used to express the findings. Results with a p value of less than 0.05 were considered statistically significant.

RESULTS

The study included 64 vitiligo patients and 20 healthy controls, for a total of 84 participants. Table 1 displays descriptive information on the participants' age and gender, as well as the duration of the illness in vitiligo patients.

Table 1. The descriptive statistics for the patient and control groups.

	Vitiligo Patients	**Control Group**
N	64	20
Age (years), mean (SD)	29.1 (11.2)	27.9 (10)
Female, n (%)	30 (46.9)	9 (45)
Male, n(%)	34 (53.1)	11 (51)
Duration of illness (months), mean (SD)	108.42 (98.2)	–

Vitiligo patients had lower mean MDA levels than healthy controls (mean ±SD) = 12 ±19, 95% CI 7.2–16.8 vs. 33.4 ±35.9, 95% CI 16.6–50.2). Vitiligo patients also had significantly lower DNPH (mean ±SD = 2 ±3.1, 95% CI 1.2–2.7 vs. 6 ±7.4, 95% CI 2.5–9.5), 8-OHdG (mean ±SD = 11.7 ±17.9, 95% CI 7.2–16.2 vs. 32.7 ±37, 95% CI 15.3–50), and UCP2 (mean ±SD = 8.7 ±13.7, 95% CI 5.3–12.2 vs. 21.5 ±28.4, 95% CI 8.2–34.8) levels (Table 2).

Table 2. Comparison of malondialdehyde (MDA), 2,4-dinitrophenyl hydrazone (DNPH), 8-hydroxy-2′-deoxyguanosine (8-OHdG) and uncoupling protein 2 (UCP2) levels between vitiligo patients and control group.

	Vitiligo Patients		**Control Group**		**p***
	Median (IQR)	[Min.–Max.]	Median (IQR)	[Min.–Max.]	—
Malondialdehyde, ng/mL	4.4 (5.5)	[1.5 – 92]	12.9 (72.4)	[2 – 92.3]	0.003
2,4-dinitrophenyl hydrazone, ng/mL	0.9 (0.7)	[0.5 – 19.7]	2.1 (10)	[0.5 – 26.1]	0.011
8-hydroxy-2′-deoxyguanosine, ng/mL	4.7 (2.8)	[2.6 – 96.4]	10.6 (64.9)	[3.9 – 114.2]	0.002
Uncoupling Protein 2, ng/mL	3.9 (2)	[3 – 83.4]	5.8 (25.8)	[2.9 – 111.6]	0.045

* Mann-Whitney U test

DISCUSSION

We found significantly lower levels of MDA, DNPH, 8-OHdG, and UCP2 in vitiligo patients compared to healthy controls. There are conflicting findings in the literature, with various oxidative stress markers being reported as increased or decreased in vitiligo patients (2,10,17).

Malondialdehyde: MDA is formed as a result of ROS peroxidation of polyunsaturated fatty acids and is widely accepted as a biomarker of oxidative stress (14). Although it is frequently used, preanalytical (sampling, storage, artifact formation, etc.) and analytical factors (choosing the appropriate measurement method) should be taken into account in order to achieve accurate results (14). Speeckaert et al. conducted a meta-analysis and concluded a significant increase in MDA levels in vitiligo patients, but they cautioned that the high heterogeneity due to study designs may introduce bias when interpreting results (17). Another meta-analysis found that MDA levels were significantly higher in patients with active or stable vitiligo, and further subgroup analysis revealed that this significance was maintained in serum, plasma, whole blood, and skin samples but not in erythrocytes (24). They also reported similar sample size and heterogeneity limitations, as well as publication bias in MDA-related studies (24).

2,4-dinitrophenyl hydrazine: DNPH is generated by the derivatization of protein side chain carbonyl groups by 2,4-dinitrophenylhydrazine and is one of the most commonly used protein oxidation markers (15,20). While the samples are easy to store and analyze due to their chemical stability, the disadvantage is that the measurement cannot differentiate which ROS are produced and which proteins are damaged specifically (15). Given that proteins have distinct biological activities and that oxidative stress-induced diseases are triggered by the loss of function in a specific protein, protein carbonyl levels alone are insufficient to explain specific disease processes (15). However, it is still widely used and has been linked to various disorders such as Alzheimer's, diabetes, and inflammatory bowel disease (15).

A study indicated that DNPH levels in the whole blood of active and stable vitiligo patients were high but comparable to healthy controls, while no significant level was reported (25). According to the same study, plasma levels of another protein oxidation marker, advanced oxidation of protein products, are comparable as well (25). Other studies have found that serum levels of advanced oxidation of protein products are comparable (26) or increased (27,28) in vitiligo patients. The oxidised form of tyrosinase protein, which plays an important role in melanin synthesis, was found to be significantly higher in vitiligo patients (28). Studies on protein oxidation products in vitiligo patients are scarce, and they are hampered by heterogeneity in study designs, which is a common limitation of oxidative stress studies.

8-hydroxy-2′-deoxyguanosine: Guanine is the most easily oxidized nucleic acid base, and the oxidation product 8-OHdG is a widely established biomarker of ROS-induced DNA damage (29). 8-OHdG can be produced as a result of DNA damage in the nucleus or mitochondria (29,30). Despite using different analytical methodologies, studies in vitiligo patients observed higher amounts of 8-OHdG in whole blood (31), mononuclear leukocytes (32), serum (33), and skin (33) samples. Both nuclear and mitochondrial DNA are damaged in vitiligo patients (34), and a genetic polymorphism in the apurinic endonuclease 1 enzyme, which is responsible for the DNA base excision repair pathway, has been linked to the risk of vitiligo (35). It has been postulated that mitochondrial DNA damage causes instability, which results in increased ROS production and a compensatory rise in mitochondri and mitochondrial DNA quantities (31).

Although the results of the studies in this field are similar, the paucity of data and significant differences in the study designs, such as differing analytical methods, appear to be limitations.

Uncoupling Protein 2: Uncoupling proteins are transport proteins found in the inner membrane of mitochondria (36). UCP1 was initially identified as a protein that generates heat rather than ATP when transferring H+ ions from the intermembranous area to the mitochondrial matrix (37). UCP2, on the other hand, has been discovered as a transport protein that upregulates in response to oxidative stress caused by ROS, lipid peroxidation products, and other alkenals, and restricts mitochondrial ROS generation (11,22,38,39). UCP2 is a marker of increased oxidative stress that has been linked to cancer (37), diabetes, obesity, degenerative diseases, and aging (22). Although UCP2 proteins have been found to function in the skin (40), data on UCP2 levels in vitiligo patients is limited. Although our study demonstrated a significant decrease in serum UCP2 levels in active vitiligo patients compared to healthy controls, more research is needed to draw conclusive results.

Strengths and Limitations: While the study's strengths include the simultaneous evaluation of common ROS targets such as lipids, proteins, and nucleic acids, using analytical methods consistent with those previously reported in the literature, and enrolling a large number of active vitiligo patients, there are some significant limitations that should be acknowledged in our research and oxidative stress research in general.

The heterogeneity of methodology, which is a common problem in oxidative stress research, is a major limiting factor that we encounter in both independent studies and meta-analyses (16,24). The lack of standardization in the enrollment of the patient (active or stable, localized or generalized vitiligo) and control groups, the sampling (plasma, serum, whole blood, skin, etc.) and storage preferences, and most importantly, the selection of analytical methods makes it difficult to interpret the results together (14,16).

There are several oxidative stress indicators, and they may be implicated in the underlying pathophysiology of various diseases; establishing which one is associated with which disease is a work in progress. Due to the lack of a defined analytical method and the inability to determine reference values, oxidative stress markers are not suitable for routine use or diagnosis (14,16). Furthermore, aside from the unique underlying pathogenetic processes of the diseases, oxidative stress markers may rise owing to non-specific factors (alcohol, tobacco, drugs, air pollutants, UV radiation, certain foods, metals, and industrial solvents, etc.) (8,16,19). It should be noted that in studies with small sample sizes, there may be increases in oxidative stress markers associated with unanticipated non-specific processes in both the patient and control groups, and caution should be exercised when drawing conclusions. Larger sample size studies employing mutual analytical methods will aid in understanding the role of oxidative stress in the pathophysiology of vitiligo.

CONCLUSION

In recent decades, reactive oxygen derivatives and oxidative stress research have become popular yet contentious topics. There have been several reports of elevated oxidative stress markers in systemic disorders such as diabetes and chronic kidney disease (16), as well as skin diseases such as vitiligo, psoriasis, atopic dermatitis, lichen, and urticaria (17). Although there is substantial evidence that oxidative stress has a role in vitiligo, it is unclear whether increased ROS markers are primarily responsible or specific for the disease's underlying pathophysiology (16,17). Although the majority of research is done on serum or plasma samples, studies that analyze the oxidative stress markers in skin samples (41) may be considered a more realistic model for oxidative stress research due to the ease of access to the tissue where the pathophysiology primarily occurs. Furthermore, research on both skin and blood samples in the same subjects will pave the way for a better understanding of the disease process. More research is needed to determine the precise mechanism of oxidative stress in the pathophysiology of vitiligo. The data obtained might lead to future targeted antioxidant therapies.

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RESEARCH ARTICLE

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Clinicopathologic Characteristics of Gastrointestinal Stromal Tumors and Prognostic Importance of Ki-67 Labeling Index: May be a New Prognostic Marker

ABSTRACT

Objective: The biological behavior of gastrointestinal stromal tumors (GISTs) varies widely and it is diffucult to predict their malignant potential with the current risk classification criterias. Therefore, we aimed to analyse the prognostic importance of Ki-67 LI for estimating survival outcomes in patients with GISTs.

Methods: For the last 11 years, between 2006 and 2017, who had been treated after surgery were included. A single pathologist re-defined the histologic examples of all cases retrospectively.

Results: Totally, 104 patients were included in the study. The median follow-up time was 73 months (range; 6 to 148 months). Seven of the 104 patients (7%) had local recurrence, 26 of the 104 patients (25%) had distant metastases and 11 of the 104 patients (11%) died during the follow-up period. The mean OS was 133 (range; 124 to 141) and the mean DFS was 117 (range; 107 to 127) months for patients. The disease progression or recurrence during follow up and increasing age were the significant prognostic factors for OS. Mitotic count, growth pattern, tumor location and Ki-67 LI were the significant prognostic factors for DFS. According to multivariate analyses, the Ki-67 LI was the only prognostic factor for estimating disease progression or recurrence (p=0.04).

Conclusions: The most important prognostic factors that affect OS were the age and disease progression or recurrence of disease. Ki-67 LI was the only prognostic factor for estimating disease progression or recurrence. As the follow-up period increases, we think that Ki-67 LI also will affect overall survival.

Keywords: Gastrointestinal Stromal Tumors, Ki-67, Prognostic Factors, Survival.

Gastrointestinal Stromal Tümörlerin Klinikopatolojik Özellikleri ve Ki-67 proliferasyon İndeksinin Prognostik Önemi: Yeni Bir Prognostik Belirteç Olabilir

ÖZET

Amaç: Gastrointestinal stromal tümörler (GIST'ler), gastrointestinal sistemin en sık görülen mezenkimal neoplazmlarıdır. GIST' lerin biyolojik davranışı çok değişkendir ve mevcut risk sınıflandırma kriterleri ile malignite potansiyellerini tahmin etmek oldukça güçtür. Bu nedenle, çalışmamızda GIST' li hastalarda sağ kalım sonuçlarını tahmin etmek için Ki-67'nin prognostik önemini analiz etmeyi amaçladık.

Gereç ve Yöntem: 2006 ve 2017 yılları arasında cerrahi sonrası tedavi altına alınan hastalar çalışmaya dahil edildi., Tüm vakaların histolojik örnekleri geriye dönük olarak tek patolog tarafından yeniden değerlendirildi.

Bulgular: 104 hasta çalışmaya dahil edildi. Ortalama takip süresi 73 aydı (6- 148 ay). Takip süresince 104 hastanın 7' sinde (% 7) lokal nüks, 26' sında (% 25) uzak metastaz mevcut olup 11' i (% 11) ex idi. Tüm hastalar için ortalama genel sağ kalım (OS) 133 (124-140) aydı. Ortalama hastalıksız sağ kalım (DFS) 117 (107-127) aydı. Takip süresince hastalığın progresyonu, rekürrensi ve yaş artışı OS için önemli prognostik faktörlerdi. Mitoz sayısı, büyüme paterni, tümör yerleşimi ve Ki-67 indeksi DFS için önemli prognostik faktörlerdi. Çok değişkenli analizlere göre, Ki-67 hastalığın ilerlemesi veya nüksünü tahmin etmede tek prognostik faktördü (p = 0.04).

Sonuç: OS' yi etkileyen en önemli prognostik faktörler; yaş, hastalık progresyonu veya nüx idi. Ki-67, hastalık progresyonu veya nüksünü tahmin etmede tek prognostik faktördü. Bu sonuçlar ışığında takip süresi uzadıkça Ki-67'nin genel sağ kalımı da etkileyeceğini düşünüyoruz.

Anahtar Kelimeler: Gastrointestinal Stromal Tümör, Ki-67, Prognostik Faktörler, Sağ Kalım.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs), are the most common mesenchymal neoplasms of the gastrointestinal tract and arise from interstitial cells of cajal (1). These tumors are most frequently occuring in the stomach (60%), small intestine, ileum and jejunum (30%), duodenum (5%), rectum and colon (3–5%), respectively (2). The signs and symptoms of GISTs are varied, depends on tumor size and location. Abdominal distension, gastrointestinal bleeding, and vague pain are the most common clinical symptoms of disease (3).

The mainstay treatment modality for localized tumors is surgery with clear resection margins (4). The characteristics of pathologic specimens are crucial for directing adjuvan treatment and predicting the survival (5). The most significant pathological parameters for estimating prognosis are tumor size and mitosis. Fletcher et al. determined the "National Institutes of Health consensus" which defined aggressive tumors according to the mitotic count (>5mitoses/ 50HPF) and tumor size (> 5cm) accepted as high-risk characteristics (6). Gold et al. from Memorial Sloan Kettering Cancer Center (MSKCC) and Miettinen et al. from the Armed Forces Institute of Pathology (AFIP) identified two additional risk stratification systems included in tumor location as a 3th pathologic parameter related with enhanced risk of recurrence (7).

In spite of consistent data on clinicopathological features of GISTs, almost all risk stratification systems for predicting the prognostic subgroups of GISTs have some constraints in estimating survival. In this context, there is a necessity to define new prognostic markers on the purpose of predicting tumor behavior and prognosis. Immunohistochemical determination of Ki-67 is the method most widely utilized in clinical practice to evaluate the proliferative activity of cancer cells. Except for the resting phase of cell cycle (G0-phase), Ki-67 is determined in all proliferative phases (G1-, S-, G2- and M-phase) (8). Some studies showed that the percentage of Ki-67 positive cells, also named as ‘labeling index (LI)’, can be utilized for the risk stratification of GISTs (9,10). But, the prognostic value of Ki-67 index in GISTs patients is still uncertain.

In the current research, we therefore aimed to analyse the prognostic importance of Ki-67 LI in GISTs patients who were treated with definitive approachs.

MATERIAL AND METHODS

Patient Characteristics: Patients with GISTs who had been operated between 2006 and 2017 were included in this study. The excluding criterias were: follow-up time <6 months, age <18 years, Karnofsky Performance Status (KPS) < 70, a history of other type of cancer within the last 5 years and documented metastasis at the time of diagnosis. The patients who received preoperative chemo or radiotherapy were excluded from the study. Finally, the data of 104 patients with GISTs were evaluated.

This research was confirmed by the board of our university and complied with the Declaration of Helsinki.

Treatment and Follow-up: After radical surgery, if the disease was localized primary GISTs, no adjuvant therapy was recommended. Adjuvant imatinib was recommended, if the disease was locally advanced or patients with intermediate-to-high risk disease. Patients were examined for tumor status in three month intervals for 2 years and in six month interval for 3 to 5 years, and annually thereafter. Follow-up information was collected by review of electronic inpatient records.

Histopathological Evaluation: A single pathologist (F.S.) re-defined the histologic examples of all cases retrospectively based on the guideline recommendation of the Collage of American Pathologists (CAP). Hemotoxylen-Eosine stained, formaline fixed and paraffin wax-embedded tumor slides were re-evaluated to verify tumour morphology. All the microscopic and gross characteristics of surgical specimens were recorded including primary tumor location, tumor size, number of mitosis, tumor morphology, and prognostic group. The diagnosis was comfirmed by immunohistochemistry with one of the CD-117 or DOG1. Immunohistochemical stained sections were used for the assesment of Ki-67. Only nuclear staining of Ki-67 was considered positive when scoring Ki-67. Proliferation index is identified as the percentage of positive staining cells among the total number of tumor cells in the area scored. The slides were analyzed with x4 and x10 object lenses to define the region of most intense staining. The expression level of Ki-67 index was identified by numbering at least 500 tumor cells in the high-power (x40 objective) areas. The Ki-67 LI was determined to be below or above 10%. The mitotic index was identified by numbering the count of mitotic cells per 50 HPFs.

Statistical Evaluation of Data: All statistical analyses were carried out using Statistical Package for Social Sciences software version 22.0 (SPSS, Chicago, IL, USA). Patient, treatment and disease characteristics were evaluated using descriptive statistics. The overall survival (OS) was defined as the time from surgery to the date of the death or last follow-up. The disease-free survival (DFS) was defined as the time from surgery to the date of documented recurrence/progression or to the date of death from cancer or last follow-up. Kaplan and Meier test was performed for survival analyses and two-sided log rank test was fulfilled to make comparisons between subgroups. The estimation of hazard ratios and 95% confidence intervals (CIs) were evaluated using Cox regression analysis. The parameters which had statistical significance in univariate analysis ($p < 0.05$) were added in

multivariate analysis as covariates. A p value less than 0.05 was accepted statistically significant.

RESULTS

Patients, Tumor and Treatment Characteristics: Overall, 104 patients with GISTs were included in this study. The median follow up time was 73 months (range; 6 to 148 months). The median age was 60 years (range: 29 to 88 years; median 60 years). All cases were categorised into different risk group as regards to modified NIH and AFIP risk classification systems. The detailed patients, treatment and histopathologic features of GISTs are presented in Table 1.

Table 1. Patient, tumor and treatment characteristics

Variables	No. of patients (Total:104)	%
Age (years)		
Median	60	
Range	29-88	
Sex		
Male	51	49
Female	53	51
Karnofsky Performance Status		
90-100	95	91
70- 89	9	9
Tumor Site		
Gastric	61	59
Non-gastric	43	41
Tumor size (cm)		
<2	15	14
2-5	24	23
5-10	40	39
>10	25	24
Mitotik rate		
<10	81	78
≥10	23	22
Cell Type		
Spindle	62	60
Epithelioid	12	11
Mixt	30	29
Growth Pattern		
Expansile	82	79
İnfiltrative	22	21
Atypia		
Slight	76	73
Modarate	6	21
Significant	22	6
Cellularity		
Slight	90	87
Significant	14	13
Ki-67		
<10%	67	64
≥10%	37	36
Surgical margin status		
R0	102	98
R1/R2	2	2
Postoperative Imatinib		
Yes	50	48
No	54	52

Survival Analysis: The median follow-up time was 73 months (range; 6 to 148 months). Seven of the 104 patients (7%) had local recurrence, 26 of the 104 patients (25%) had distant metastases and 11 of the 104 (11%) patients died during the follow-up period.

The mean OS was 133 (range; 124 to 141) months for all the patients. 2-, 5- and 10- year OS rates were 93%, 89% and 89%, respectively. According to univariate analysis, only the disease progression or recurrence during follow up was significant prognostic factor for OS (Fig1, p=0.001). In multivariate Cox regression analysis, the patient age and progression or recurrence of disease were independent prognostic factors for OS. Patients with increasing age had a shorter OS (p=0.03) and the older age was associated with 1.09- fold higher risk of death (p=0.03; HR: 10.9 [1.06- 1.18]). Patients who had progression or recurrence during the follow-up time had a shorter OS (p=0.002) and was associated with 27.64- fold higher risk of death (p=0.002; HR: 27.64 [3.55-215.02]).

The mean DFS was 117 months (range; 107 to 127 months) for all the patients. 2-,5- and 10- year DFS rates were 94%, 88% and 67%, respectively. According to Kaplan Meier analysis, mitotic count, growth pattern, disease location, and Ki-67 index were the significant prognostic factors for DFS. Patients with >5mitoses/ 50HPF had a poorer DFS than ≤5mitoses/ 50HPF. Kaplan Meier analysis of the mean DFS was 126 months for the patients with ≤5mitoses/ 50HPF vs 105 months for the patients with >5mitoses/ 50HPF (p=0.03; Fig 2a). Patients with infitrative growth pattern had a shorter DFS than expansile growth pattern. Kaplan Meier analysis of the mean DFS was 122 months for the patients with expansile growth pattern vs 98 months for the patients with infiltrating growth pattern (p=0.013; Fig 2b). In addition to these factors, the DFS was affected by primary tumor site. Patients with primary gastric GISTs had longer DFS than non-gastric GISTs. Kaplan Meier analysis of the mean DFS was 128 months for the patients with gastric GISTs vs 99 months for the patients with non-gastric GISTs (p=0.004; Fig 2c). Patients with a Ki-67 LI value <10% had a longer DFS than patients with a Ki-67 LI value ≥10%. Kaplan Meier analysis of the mean DFS was 131 months for the patients with a Ki-67 LI value <10% vs 103 months for the patients with a Ki-67 LI value ≥10% (p= 0.003; Fig2d). In multivariate Cox regression analysis, Ki-67 index was the only significant prognostic factor for predicting disease progression or recurrence (p=0.04). The patients who had the level of Ki-67 ≥10% had a poorer DFS and these group of patients had 3.78- fold higher risk of progression or recurrence (p=0.04; HR: 3.78 [1.05-13.61]).

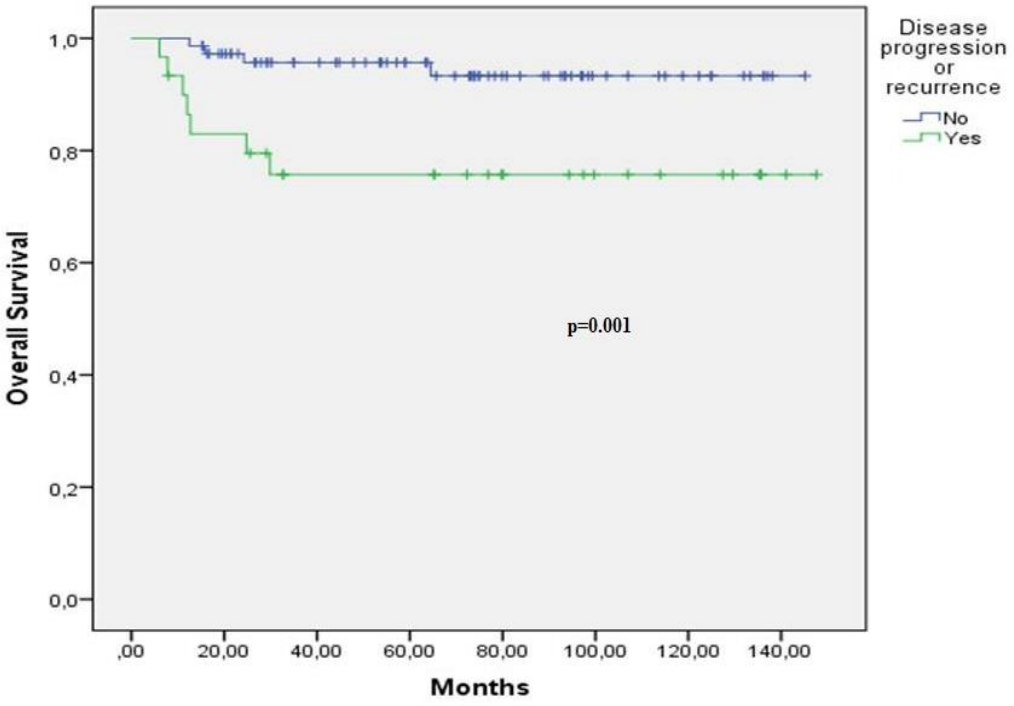

Figure 1. Overall survival according to the disease progression and recurrence.

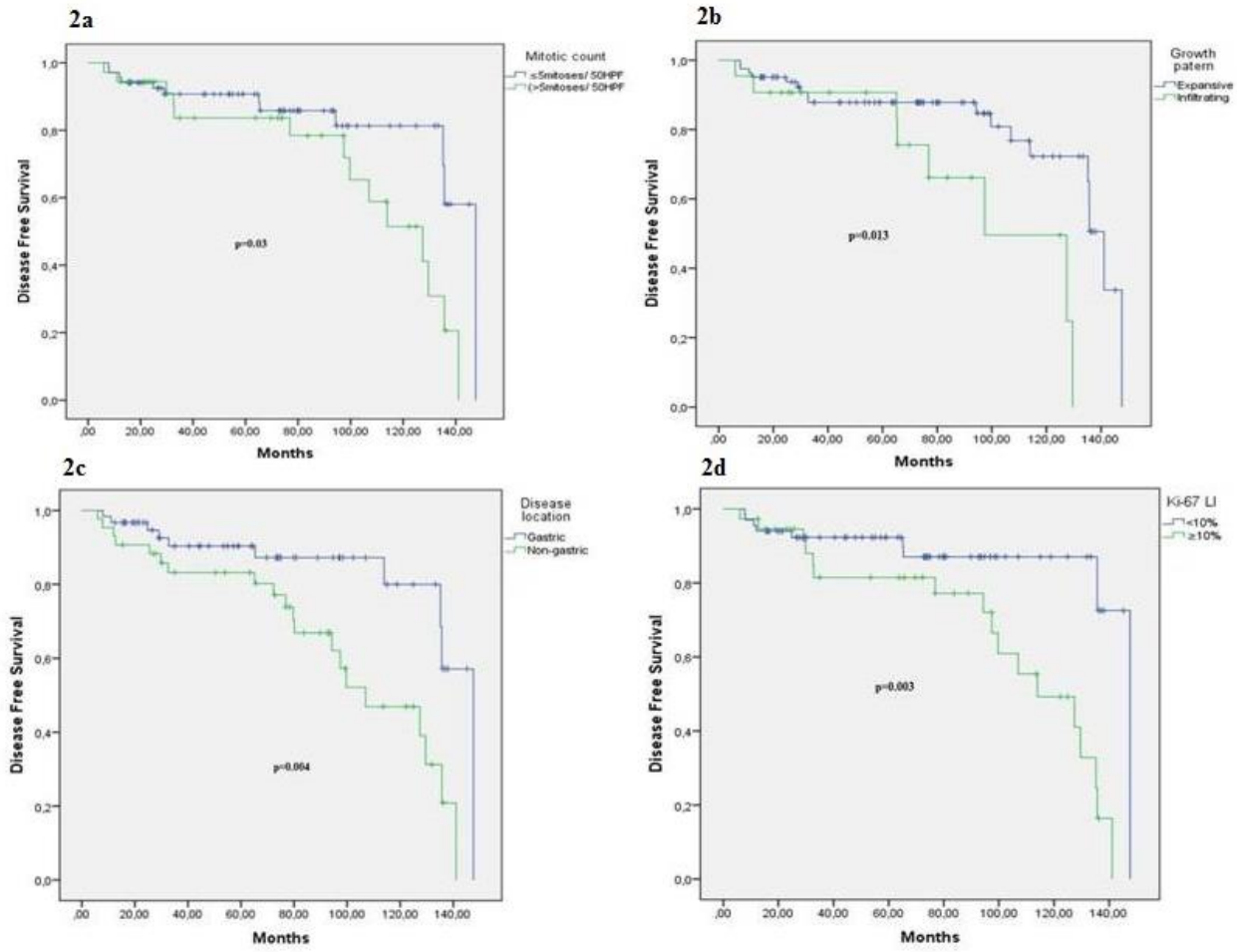

Figure 2. Disease free survival according to mitotic count (2a), growth pattern (2b), disease location (2c), and Ki-67 LI (2d).

DISCUSSION

The biological behavior of GISTs varies widely and it is diffucult to estimate their aggressiveness using the current risk classification criterias. There is a large heterogeneity exists among patients with GISTs, even those with the same risk classification. So that, the researchers continue to investigate the additional prognostic factors to improve the current risk classification criterias.

In the current study, the age and the disease progression or recurrence during follow up were significant prognostic factors for OS. Patients who had progression or recurrence during the follow-up period and older age had a shorter OS. The mitotic count, growing pattern, tumor location, and Ki-67 index were the significant prognostic parameters for DFS. Among them, only the Ki-67 index was independent prognostic factor for DFS according to multivariate analysis. It may be a signal that, as the follow-up period increases, the Ki-67 LI will affect the OS. The prognostic affect of Ki-67 LI in patients with GISTs was examined by previous researchs. But the results of these studies conflicted with each others results (9,10,19-21). Zhao et al. investigated the prognostic importance of Ki-67 LI and identified the cut-off point of Ki-67 LI as ≤5, 6-8 and >8%. They revealed that Ki-67 LI is a significant prognostic factor for recurrence free survivals and concluded that Ki-67 LI >8% can influentially subdivide high risk patients with different outcomes in the same group according to NIH criteria (19). Liu et al. divided the patients into two groups according to Ki-67 index as ≤6 or >6% and found that patients with Ki-67 index >6% had considerably shorter OS than patients with ≤6 (20). In contrast to these results, Sozutek et al. revealed that Ki-67 LI was associated with mitotic index but there was not any association between Ki-67 index and survival outcomes (21).

Besides the prognostic affect of Ki-67 LI on survival outcomes, we also investigated the other clinicopathologic factors. The prognostic importance of age was investigated in several researchs but the results of studies conflict with each others. In Chinese population, it was reported that patients over 60 years of age had a longer survival time (11) on the other hand Kramer et al. found that patients with ≥50 years displayed significantly shorter DFS compared to patients with <50 years (12). More recently, Yang et al. (2) revealed their study results which investigating the clinicopathologic characteristics and prognostic factors of GISTs and they did not find any association between the age and survival outcomes. According to our results, the patients with increasing age had a poorer OS and was associated with 1.09 fold higher risk of death.

Location of disease is the other clinicopathologic factor for GISTs. We know that, GISTs are most commonly occuring in the stomach. Some of the previous studies demonstrated that longer OS for primary gastric GISTs and non-gastric tumor location accepted to be associated with poor prognosis and tumor recurrence (2,5,7,11-13). According to our results, when comparing with the other tumor locations, patients with primary gastric GISTs had longer DFS in accordance with the literature.

The other independent parameters for determining risk groups in GISTs are tumor diameter and mitosis in reference to NIH and AFIP risk classification systems (6,7). According to our results, patients with increasing tumor diameter tended to have a shorter survival outcomes but the results did not reach significance (p=0.07). Additionally, mitotic count was determined as a significant prognostic factor for DFS. Patients with >5mitoses/ 50HPF had a poorer DFS than ≤5mitoses/ 50HPF. Invasive growth pattern of tumor was associated with poor prognosis (16-18). Miettinen and Losata developed a method to predict the risk of metastasis and recurrence which included the high cellularity, invasion and tumor rupture in addition with tumor size, disease location, and mitotic rate (7). We didn't find any association between the high cellularity and prognosis but growth pattern of tumor was the significant prognostic factors for DFS. Patients with infitrative growth pattern had a poorer DFS than expansile growth pattern.

Microscopically, three main histologic subtypes were defined: spindle cell type (most common), epithelioid type and mixed type (6,7). Some authors found that epithelioid morphology is associated with poor prognosis (14,15) and the others argued that survival rates have increased in tumors of epithelioid cell type (11). But, there was not any association between the cell type and prognosis according to our results.

We are aware of that there are some limitations of the study; including limited sample size and its retrospective nature. But, this single institution study is particulary important because all the histologic examples of cases re-defined by a single pathologist who is unaware of the survival of patients.

CONCLUSION

In conclusion; the current investigation demonstrated that the patient age and disease progression or recurrence of disease were the most important prognostic factors for OS. Ki-67 LI was the only independent prognostic factor for estimating disease progression or recurrence according to multivariate analysis. As the follow-up period increases, we think that Ki-67 LI also will affect OS. The Ki-67 LI may be a new prognostic factor for GISTs and it may be use as an effective component of current risk classification criterias. Further prospective randomized controlled studies are needed to support our study.

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RESEARCH ARTICLE

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The Relationship of Early Repolarization Morphology with Prognosis and Mortality Accompanied by Angiography Results

ABSTRACT

Objective: Early repolarization (ER) is a common finding in cases. It can be benign or malignant. We aimed to evaluate the effects of early repolarization morphology and electrocardiogram (ECG) findings on the clinic, prognosis, and mortality with angiography findings.

Methods: This retrospective study included 442 patients who were admitted to the emergency department between January 2010 and December 2015 and had ER in their ECG. The patients were divided into two groups according to the horizontal and ascending ER morphology. According to the derivation, four groups were formed as inferior, inferolateral, anterior, and common. During the five-year follow-up period, patients who had an indication for angiography due to chest pain and underwent the procedure were divided into four groups (left anterior descending (LAD), circumflex (Cx), right coronary artery (RCA), and normal) according to the vessel in which the lesion was detected in angiography.

Results: The average age of the patients in the study was 52.16±9.07 years and 260(58.8%) were male. Horizontal morphology was observed in 123(28%) of the patients and ascending morphology in 319(72%). Mortality was detected in 9(7.3%) of the horizontal group and 6(1.9%) of the ascending group (p=0.008). In the angiography results of the mortality group, 8(53.3%) patients had Cx, 4(26.7%) patients had RCA, and 3(20%) patients had LAD occlusion. Angiography results of 318(74.5%) surviving patients were normal (p=0.001). Mortality; It had a strong positive correlation with family history, Brugada Syndrome, aVR ST-segment formation and the presence of syncope, and moderate positive correlation with gender, notch presence, QRS morphology in V1-2, and angiography results.

Conclusions: Early repolarization morphology may be a helpful finding for prognosis, mortality, and interventional angiography decisions.

Keywords: Emergency Department, Early Repolarization, Mortality, Angiography.

Erken Repolarizasyon Morfolojisinin Anjiyografi Sonuçları Eşliğinde Prognoz ve Mortalite ile İlişkisi

ÖZET

Amaç: Erken repolarizasyon (ER) sık görülen bir bulgudur. Benign ya da malign karakterde olabilir. Erken repolarizasyon morfolojisi ve elektrokardiyogram (EKG) bulgularının anjiyografi bulguları ile klinik, prognoz ve mortalite üzerine etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmaya Ocak 2010 ile Aralık 2015 arasında acil servise başvuran ve EKG'sinde ER olan 442 hasta dahil edildi. Hastalar ER morfolojisinin yatay ve dikey olmasına göre iki gruba ayrıldı. Derivasyona göre ise inferior, inferolateral, anterior ve yaygın olmak üzere dört grup oluşturuldu. Ayrıca anjiyografi bulgularına göre sol ön inen (LAD), sirkumfleks (Cx), sağ koroner arter (RCA) ve normal olmak üzere dört grup belirlendi.

Bulgular: Çalışmaya alınan hastaların yaş ortalaması 52.16±9.07 yıl ve 260'ı (%58.8) erkekti. Hastaların 123'ünde(%28) yatay, 319'unda(%72) dikey morfoloji izlendi. Yatayl grupta 9(%7.3) ve dikey grupta 6(%1.9) olguda mortalite saptandı (p=0.008). Mortalite grubunun anjiyografi sonuçlarında 8 (%53,3) hastada Cx, 4 (%26,7) hastada RCA ve 3 (%20) hastada LAD oklüzyonu vardı. Yaşayan 318 (%74,5) hastanın anjiyografi sonuçları normaldi (p=0,001). Mortalitenin; aile öyküsü, brugada sendromu, aVR ST-segment varlığı ve senkop ile güçlü, cinsiyet, notch varlığı, V1-2'de QRS morfolojisi ve anjiyografi sonuçları ile orta düzeyde pozitif korelasyonu tespit edildi.

Sonuç: Erken repolarizasyon morfolojisi, prognoz, mortalite ve girişimsel anjiyografi kararları için yardımcı bir bulgu olabilir.

Anahtar Kelimeler: Acil Servis, Erken Repolarizasyon, Mortalite, Anjiyografi.

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INTRODUCTION

Early repolarization (ER) is defined as the positive J wave that starts with notching at the end of the R wave in the 12-lead electrocardiogram (ECG) recording, and the ST-segment elevation of 0.1 mV or more in at least two consecutive leads following the J wave. It is a finding seen in society with a rate of 12% and frequently encountered in the clinic. The frequency of early repolarization decreases with advancing age and is observed more frequently in healthy, young, male, and athletic individuals. Its prevalence in African and African Americans is higher than in other societies (1,2). This ECG finding is often seen in the inferior and precordial leads. While early repolarization has been considered as an innocent ECG finding for many years, recent studies have shown that this change has some potential arrhythmogenic effects (3,4).

The majority of patients are asymptomatic and have a low risk of arrhythmia. It is very important to identify the small patient group with high arrhythmic risk. To date, most of the research on this topic has evaluated variants of the ER model that increase the risk of sudden death. In studies conducted, the presence of J waves and ST-segment elevation on the ECG, which is called early repolarization pattern, has been accepted as a benign finding without clinical significance (5,6). It is very important to distinguish benign ER, which is very common, from the rare malignant form. Recently, two ER morphologies, ascending and horizontal, have been emphasized in determining the severity of early repolarization (7,8). An image describing ascending and horizontal ER morphologies is given in Figure 1 (9). While these criteria are valuable in predicting fatal arrhythmias in elderly patients, they are insufficient in predicting ventricular arrhythmia and sudden cardiac death in young patients. Genetic predisposition is important in ER patients with idiopathic sudden cardiac death. Studies have found that patients with ER in the inferior and lateral leads have a higher genetic predisposition. In cases where ER is detected in patients with fatal arrhythmia symptoms or a family history of sudden cardiac death, it is very important to evaluate and perform further examination (10-12).

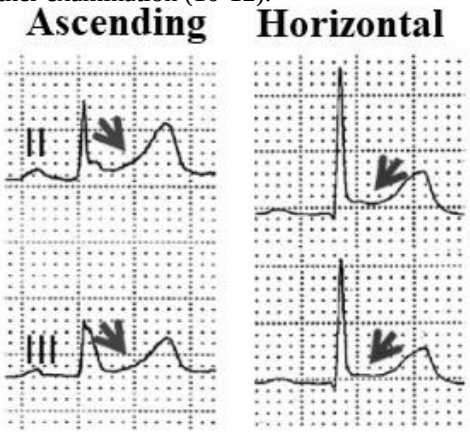

Figure 1. Ascending and horizontal ER morphologies (9)

In the differential diagnosis, it is important to distinguish ER from ST-segment elevation conditions such as asthenic habitus, acute pericarditis, ST-elevation myocardial infarction, Brugada Syndrome, congenital short QT syndrome, and idiopathic ventricular fibrillation. Congenital long QT syndrome without ST-segment elevation but causing syncope and sudden cardiac death and catecholaminergic polymorphic ventricular tachycardia (VT) should also be included in the differential diagnosis. It is necessary to distinguish between these pathologies and ER.

It is very important to determine the ECG features that distinguish the benign ER model from the malignant ER. In our study, we aimed to contribute to the literature on distinguishing benign and malignant ER by associating the demographic characteristics, ECG findings, laboratory values, mortality rates, and especially the results of coronary angiography, which has not been evaluated until now, with the ER pattern.

MATERIAL AND METHODS

Study Design and Population: In this retrospective study, 442 patients (182 females, 260 males; average age 52.2 ± 9.1 years; range 23-72 years, 41.2% females) over 18 years old who presented to the emergency department between January 2010 and December 2015 and had early repolarization in their ECG were included.

Patients with severe heart valve diseases, rhythm disturbances, history of by-pass operation, cerebrovascular disease, ECG changes due to subarachnoidal hemorrhage, chronic liver disease, chronic renal failure, malignancy, aortic dissection, pneumothorax, pulmonary pathologies causing ECG changes, myocardial infarction, and related aneurismatic appearance, and electrolyte imbalance were excluded from the study. Patients diagnosed with early repolarization were angiographed during the follow-up period and evaluated by two experienced cardiologists who were blinded to the study. Inconsistencies were resolved by consensus, and these patients were included in the study.

For all ER patients, four groups were created as inferior (DII, DIII, aVF), inferolateral (DII, DIII, aVF, V3-6), anterior (V1-6), and common (DII, DIII, aVF, aVL, V1-6) (13). In addition, ER cases were divided into two groups according to their morphology as horizontal and ascending. Patients were also divided into two groups according to their mortality status. Patients who had an indication for angiography due to chest pain and underwent the procedure were divided into four groups (left anterior descending (LAD), circumflex (Cx), right coronary artery (RCA), and normal) according to the vessel in which the lesion was detected in angiography

Demographic, clinical, and laboratory data, along with diagnoses, admission dates, contact

information, are available in the registry system of our hospital. In our study, while the follow-up of the patients was done through the hospital registry system, those who did not re-enter the hospital were reached via the call system. Finally, after the first diagnosis of ER, patients were followed up for an average of 60 months and their results were recorded.

Electrocardiography; When the patient was admitted to the emergency department, a 12-lead ECG was obtained at the bedside with Cardiofax ECG-9132K (Nihon Kohden, Tokyo, Japan).

The study was conducted in accordance with the Helsinki Declaration on Human Research after obtaining Institutional Local Ethics approval. After all patients were informed, their consent for inclusion was obtained.

Statistical Analysis: The data obtained from the study were analyzed with the SPSS 20 (SPSS Inc., Chicago, IL, USA) package program. Kolmogorov-Smirnov test was used while investigating the normal distribution of variables. Descriptive statistics were presented as mean ± standard deviation or median (minimum-maximum) for continuous variables and as the number of cases and percentage (%) for nominal variables. While examining the differences between groups, Mann-Whitney U and Kruskal-Wallis H tests were used because the variables were not normally distributed. Chi-square analysis was used when examining the relationships between groups of nominal variables. Spearman's rho analysis was used for the correlation of early repolarization with variables. When interpreting the results, values below the significance level of 0.05 were considered statistically significant.

RESULTS

The mean age of the 442 patients in the study was 52.16 ± 9.07 years and 182 (41.2%) of them were women. In the ER classification; 242 (54.7%) were in the inferior group, 83 (18.8%) in the inferolateral, 100 (22.6%) in the anterior, and 17 (3.8%) in the common group. Of the inferior group patients, 138 (31.2%) were male and 104 (23.4%) were female. There was no significant relationship between these groups with gender and laboratory parameters (Table 1).

Table 1. Basal and laboratory findings according to the early repolarization types of the patients

		Early Repolarization				
	All patients n:442(%) mean±SD	**Inferior n:242(%) mean±SD**	**Inferolateral n:83(%) mean±SD**	**Anterior n:100(%) mean±SD**	**Common n:17(%) mean±SD**	***p-value***
Baseline characteristics						
Mean age (year)	52.16±9.07	51.70±9.05	52.36±8.96	53.21±8.98	51.47±10.64	0.565
Famale	182(41.2)	104(23.4)	35(7.9)	37(8.4)	6(1.4)	0.724
Male	260(58.8)	138(31.2)	48(10.9)	63(14.3)	11(2.5)	
Laboratory Findings						
BS (mg/dl)	141.00±63.52	139.75±61.74	150.01±69.93	137.71±65.47	134.23±40.74	0.259
AST (U/L)	35.31±20.44	35.21±20.11	35.67±20.36	34.92±21.51	34.44±21.70	0.384
ALT (U/L)	33.48±23.82	33.72±22.71	34.01±22.38	33.78±23.39	34.51±22.67	0.412
Cho (mg/dl)	172.57±51.39	170.25±51.92	174.69±59.36	175.81±45.50	176.18±33.79	0.567
TG (mg/dl)	148.18±89.63	144.85±84.02	163.12±103.41	137.07±82.09	188.06±121.65	0.257
HDL (mg/dl)	35.38±7.81	35.32±7.43	35.89±9.67	35.14±7.12	35.12±7.17	0.990
LDL (mg/dl)	105.11±36.95	103.08±36.88	106.95±35.74	109.27±36.47	100.70±46.44	0.419
VLDL(mg/dl)	33.03±27.15	32.88±27.28	32.64±21.75	32.81±31.61	38.23±2.75	0.376
RDW (%)	15.09±3.70	15.16±4.26	14.96±1.88	14.86±3.21	16.05±4.62	0.167
MPV(fL)	8.51±0.89	8.48±0.90	8.59±0.88	8.53±0.87	8.60±.91	0.815
MCHC(g/dL)	33.78±6.64	33.25±4.05	34.95±10.35	34.13±8.10	33.56±1.11	0.126
MCV (fL)	85.87±9.22	86.44±7.83	86.70±5.22	83.74±12.78	84.69±15.09	0.687

SD; Stanndard Deviation, BS: Blood Suger, AST:Asptartate aminotransferase; ALT: Alanine aminotransferase, Cho: Cholesterol, TG: Triglyceride, HDL: High Density Lipoprotein, LDL: Low High Density Lipoprotein, VLDL:Very Low Density Lipoprotein, RDW: Red cell distrubition width, MPV:Mean Platelate Volum; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV; Mean Corpuscular Volume; **P<0.05**

The ST-segment in aVR was normal in 272 (85.5%) of all patients, whereas 17 (38.6%) of the Cx group had elevation (p = 0.001). QRS complex was found to be positive in V1-2 in 21 (47.7%) patients in the Cx group. 181 (56.9%) of the patients with normal angiography results were in the inferior group. However, ER was detected in the anterior in 18 (51.4%) of the LAD group, inferolateral in 18 (40.9%) of the Cx group, and inferior in 41 (91.1%) of the RCA group (p = 0.001). Syncope was present in 11 (24.4%) of the patients in the RCA group. Ascending morphology was detected in 262 (82.4%) of the patients with normal angiography results. Horizontal morphology was observed in 15 (42.9%) of the patients in the LAD group, 26 (59.1%) of the Cx group, and 26 (57.8%) of the RCA group (p = 0.001).

Mortality was most common in 8 (18.2%) patients in the Cx group, 4 (8.9%) in the RCA group, and 3 (8.6%) in the LAD group. Mortality could not be detected in patients with normal angiography results (p = 0.001, Table 2).

Table 2. Table of variables according to angiography result

Variables		Angiography Normal n(%) 318(71.9)	LAD n(%) 35(7.9)	Cx n(%) 44(10)	RCA n(%) 45(10.2)	P Value
Gender	Female	140(44)	13(37.1)	11(25)	18(40)	0.108
	Male	178(56)	22(62.9)	33(75)	27(60)	
aVR	Normal	272(85.5)	23(65.7)	22(50)	27(60)	**0.001**
	ST Elevation	35(11)	5(14.3)	17(38.6)	12(26.7)	
	ST Depression	11(3.5)	7(20)	5(11.4)	6(13.3)	
V1-V2	Normal	211(66.4)	17(48.6)	14(31.8)	20(44.4)	**0.001**
	QRS (-)	41(12.9)	8(22.9)	9(20.5)	12(26.7)	
	QRS (+)	66(20.8)	10(28.6)	21(47.7)	13(28.9)	
ER	Inferior	181(56.9)	8(22.9)	12(27.3)	41(91.1)	**0.001**
	Inferolateral	59(18.6)	2(5.7)	18(40.9)	4(8.9)	
	Anterior	68(21.4)	18(51.4)	14(31.8)	0(0)	
	Common	10(3.1)	7(20)	0(0)	0(0)	
Syncope	No	313(98.4)	28(80)	35(79.5)	34(75.6)	**0,001**
	Yes	5(1.6)	7(20)	9(20.5)	11(24.4)	
Morfology	Horizontal	56(17.6)	15(42.9)	26(59.1)	26(57.8)	**0.001**
	Ascending	262(82.4)	20(57.1)	18(40.9)	19(42.2)	
Family History	No	306(96.2)	24(68.6)	24(54.5)	29(64.4.)	**0.001**
	Yes	12(3.8)	11(31.4)	20(45.5)	16(35.6)	
Notch	No	281(88.4)	18(51.4)	32(72.7)	21(46.7)	**0.001**
	Yes	37(11.6)	17(48.6)	12(27.3)	24(53.3)	
Brugada Syndrome	No	302(95)	27(77.1)	34(77.3)	35(77.8)	**0.001**
	Yes	16(5)	8(22.9)	10(22.7)	10(22.2)	
Mortality	No	318(100)	32(91.4)	36(81.8)	41(91.1)	**0.001**
	Yes	0(0)	3(8.6)	8(18.2)	4(8.9)	

LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery, aVR: Augmented Voltage Right, V1-V2: Leads V1 and V2 in electrocardiography ER: Early Repolarization ST: The distance between S and T on electrocardiography QRS (-): The area under the isoelectric line of the distance between Q, R and S in electrocardiography, QRS (+): The area above the isoelectric line of the distance between Q, R and S in electrocardiography, P<0.05

The relationship between early repolarization groups and syncope, family history, presence of a notch, Brugada Syndrome, mortality was significant. Syncope was most frequently observed in 16 (6.6%) of the inferior group, however, although the number of cases was low, it was found with a higher rate in 5 (29.4%) patients of the common group (p = 0.001). Horizontal morphology was seen most frequently in 6 (35.3%) of the common group and at least in 17 (17%) patients of the anterior group (p = 0.004). In the Common group, 8 (47.1%) patients had notch and 4 (23.5%) had Brugada syndrome. Mortality was observed most frequently in 8 (9.6%) patients in the inferolateral group (Table 3).

Table 3. Chi-square analysis of early repolarization according to variables

Variables		Early repolarization Inferior n(%)	Inferolateral n(%)	Anterior n(%)	Common n(%)	*p-value*
aVR	Normal	190(478.5)	57(68.7)	84(84)	13(76.5)	0.378
	ST Elevation	37(15.3)	18(21.7)	11(11)	3(17.6)	
	ST Depression	15(6.2)	8(9.6)	5(5)	1(5.9)	
V1-V2	Normal	139(57.4)	48(57.8)	60(60)	15(88.2)	0.345
	QRS (-)	41(16.9)	12(14.5)	16(16)	1(5.9)	
	QRS (+)	62(25.6)	23(27.7)	24(24)	1(5.9)	
Syncope	No	226(93.4)	75(90.4)	97(97)	12(70.6)	**0.001**
	Yes	16(6.6)	8(9.6)	3(3)	5(29.4)	
Morphology	Horizontal	66(27.3)	34(41)	17(17)	6(35.3)	**0.004**
	Ascending	176(72.7)	49(59)	83(83)	11(64.7)	
Family History	No	215(88.8)	71(85.5)	86(86)	11(64.7)	**0.042**
	Yes	27(11.2)	12(14.5)	14(14)	6(35.3)	
Notch	No	200(82.6)	70(84.3)	73(73)	9(52.9)	**0.005**
	Yes	42(17.4)	13(15.7)	27(27)	8(47.1)	
Brugada Syndrome	No	229(94.6)	67(80.7)	89(89)	13(76.5)	**0.001**
	Yes	13(5.4)	16(19.3)	11(11)	4(23.5)	
Mortality	No	237(97.9)	75(90.4)	99(99)	16(94.1)	**0.013**
	Yes	5(2.1)	8(9.6)	1(1)	1(5.9)	

aVR: Augmented Voltage Right, ST: The distance between S and T on electrocardiography, V1V2: Leads V1 and V2 in electrocardiography, QRS (-): The area under the isoelectric line of the distance between Q, R and S in electrocardiography, QRS (+): The area above the isoelectric line of the distance between Q, R and S in electrocardiography, P<0.05

When early repolarization morphology groups were evaluated, horizontal morphology was observed in 123 (28%) of the patients and ascending morphology in 319 (72%). ST-elevation in aVR was present in 27 (8.3%) patients in the ascending group and in 42 (34.1%) patients in the horizontal group (p = 0.001). While the QRS complex in V1-2 was evaluated as normal in 235 (73.7%) of the ascending group, it was most frequently detected in the horizontal group in the positive direction and in 57(46.3%) patients (p=0.001). Of the horizontal group patients, 26 (21.1%) had syncope, 52(42.3%) had a family history, 42 (34.1%) had notch, and 35 (28.5%) had Brugada syndrome. In the ascending group, 6 (1.9%) had syncope, 7 (2.2%) had a family history, 48 (15%) had a notch, and 9 (2.8%) had Brugada syndrome. While mortality was observed in 9 (7.3%) of the horizontal group, it was observed in 6 (1.9%) of the ascending group (p = 0.008, Table 4).

Table 4. Chi-square analysis of early repolarization morphological structure according to variables

Variables		Early Repolarization Morphology		
		Horizontal n:123(%)	**Ascending n:319(%)**	***p-value***
aVR	Normal	59(48)	285(89.3)	**0.001**
	ST Elevation	42(34.1)	27(8.3)	
	ST Depression	22(17.9)	7(2.2)	
V1V2	Normal	27(22)	235(73.7)	**0.001**
	QRS (-)	39(31.7)	31(9.7)	
	QRS (+)	57(46.3)	53(16.6)	
Syncope	No	97(78.9)	313(98.1)	**0.001**
	Yes	26(21.1)	6(1.9)	
Family History	No	71(57.7)	312(97.8)	**0.001**
	Yes	52(42.3)	7(2.2)	
Notch	No	81(65.9)	271(85)	**0.001**
	Yes	42(34.1)	48(15)	
Brugada Syndrome	No	88(71.5)	310(97.2)	**0.001**
	Yes	35(28.5)	9(2.8)	
Mortality	No	114(92.7)	313(98.1)	**0.008**
	Yes	9(7.3)	6(1.9)	

aVR: Augmented Voltage Right, ST: The distance between S and T on electrocardiography, V1V2: Leads V1 and V2 in electrocardiography, QRS (-): The area under the isoelectric line of the distance between Q, R and S in electrocardiography, QRS (+): The area above the isoelectric line of the distance between Q, R and S in electrocardiography, P<0.05

In the mortality group, 9 patients (60%) had ST-elevation in the lead aVR, 10 (66.7%) had QRS positivity in V1-2, 11 (73.3%) had syncope, 12 (80%) had a family history, 9(60%) had Notch and 9 (60%) had Brugada syndrome (p = 0.001 Table 5).

Table 5. Chi-square analysis of mortality according to variables

Variables		Mortality		
		No n:427(%)	**Yes n:15(%)**	***p-value***
aVR	Normal	343(80.3)	1(6.7)	**0.001**
	ST Elevation	60(14.1)	9(60)	
	ST Depression	24(5.6)	5(33.3)	
V1-V2	Normal	261(61.1)	1(6.7)	**0.001**
	QRS (-)	66(15.5)	4(26.7)	
	QRS (+)	100(23.4)	10(66.7)	
Syncope	No	406(95.1)	4(26.7)	**0.001**
	Yes	21(4.9)	11(73.3)	
Family History	No	380(89)	3(20)	**0.001**
	Yes	47(11)	12(80)	
Notch	No	346(81)	6(40)	**0.001**
	Yes	81(19)	9(60)	
Brugada Syndrome	No	392(91.8)	6(40)	**0.001**
	Yes	35(8.2)	9(60)	

aVR: Augmented Voltage Right, ST: The distance between S and T on electrocardiography, V1-V2: Leads V1 and V2 in electrocardiography, QRS (-): The area under the isoelectric line of the distance between Q, R and S in electrocardiography, QRS (+): The area above the isoelectric line of the distance between Q, R and S in electrocardiography, P<0.05

DISCUSSION

There are many studies in the literature on early repolarization. However, we did not find a study in which variables and risk factors were so high, and the effect of the horizontal and ascending structure of the ER on mortality was evaluated with angiography findings. In our study, we showed that correct recognition and interpretation of ER types can independently predict the prevention of unnecessary invasive angiography in patients. Although it is always thought optimistically about ER, it has recently been reported that it may be malignant and even be associated with sudden cardiac death (14). The pathophysiological mechanisms explaining the relationship of early repolarization with ventricular arrhythmias have not been fully elucidated. Experimental studies indicate that increased transmural heterogeneity increases ventricular repolarization and this contributes to elevation at the J point (15). It may also affect ER-related ventricular arrhythmias in the autonomic system because it has been reported that a significant number of events occur more frequently during increased vagal tone or after eating too much (16,17). However, situations in which adrenergic stimulation is triggered, such as exercise, can suppress ER and associated arrhythmias (18).

Morphology of the ST segment provides important diagnostic and prognostic information in early repolarization (1,19,20). Therefore, differentiating the common benign ER from the malignant form, which is rare but can be fatal, is very important in terms of clinical prognosis and mortality (21). James et al. (22) stated in the study that ER was observed more frequently in adolescents and men and this difference may be due to gonadal steroids. Antzelevitch et al. (23) made a classification based on ECG leads kept with arrhythmia risk. Type 1 was considered benign among healthy male athletes in the lateral precordial leads (V5, V6). In Type 2, it occurs in the inferior (II, III, aVF) or inferolateral leads and is associated with moderate risk. Type 3 was considered to have the highest relative risk and was associated with an early repolarization pattern commonly localized in the inferior, lateral, and right-sided leads. Hünük et al. (24), in their study evaluating 504 male patients, found 34 ER findings ECG and showed that 19 of them were in the lateral derivation. In our study, the majority of the patients were male, but the ER was more frequently observed in the inferior lead.

The morphology of early repolarization is when there is a 0.1 mV rise in the ST segment within 100 ms after the J point, and when the ST segment gradually joins the T wave, it is considered an ascending pattern and is considered a benign form. In malignant morphology, 0.1 mV ST-segment elevation occurs within 100 ms after the J point and continues straight until the beginning of the T wave and is known as the horizontal pattern (7,8). Wasserburger et al. (25) defined ER as an ST-segment elevation accompanied by descending concavity of the ST segment at the junction of the QRS complex and suggested that this is a normal variant. Tikkanen et al. (1) showed that ER with a horizontal / descending ST-segment is associated with an increased risk of sudden cardiac death in the general population compared to the ascending segment. Uberoi et al. (26) stated in their study that the ascending ST segment was not associated with mortality in ER. Rosso et al. (8) showed that ER with horizontal ST segments was associated with sudden cardiac death in their study. Similar to the studies performed, ST-segment elevation and mortality were more frequent in aVR in our horizontal group patients.

Sinner et al. (27) demonstrated in their study that there was a strong relationship between ER and cardiac mortality, and this relationship was greater especially in inferior leads. In the same study, they found that ER has a strong relationship with mortality due to cardiac and noncardiac causes. Syncope and family history were higher in the group in which mortality was observed in our study. We attribute this to the genetic effects of cardiac mortal pathologies and the fact that syncope is a symptomatic stimulus in patients. We can also consider the presence of ST elevation in aVR and positive QRS in V1-2 as a stimulus for mortality. In addition, although the risk factors mentioned in the studies were evaluated, we did not find any association according to the angiography results of the patients. Occlusion was detected in more than half of the angiography results in the horizontal ER formation showing a malignant pattern. On the other hand, angiography findings were mostly normal in ascending form. LAD, Cx, and RCA involvements were close to each other, but angiography findings were significantly positive in the horizontal form. We think this is because the prognosis of the horizontal form is worse and more malignant. In the study, the absence of normal angiography results in any of the patients with mortality may be evidence of the relationship between angiography findings and mortality. In addition, more Cx occlusion in patients as a result of angiography may be parallel with high inferior and inferolateral mortality. We think that the relationships of our angiography findings with the ER derivation originate from the vascular distribution localizations of the heart.

CONCLUSION

In the horizontal morphology of early repolarization, positive angiography findings and higher mortality should be a warning situation for the clinician. Besides, it can be said that the presence and shape of the ER in the ECG is a guide for the prognosis, mortality and angiography of the patients. More prospective studies are needed on early repolarization.

The most important limitations of the study are that it is single-centered, retrospective, difficult

to follow-up for 5 years, and we do not have data on diabetes, hypertension and smoking histories of the patients.

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Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards. Necessary ethics committee approval was obtained for this study.

We confirm that the authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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RESEARCH ARTICLE

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Using Smartphone to Evaluate Cranial Computed Tomography Videos: An Inter-Observer Study

ABSTRACT

Objective: Many clinicians receive Cranial Computed Tomography (CCT) images or videos by their smartphone. The aim of this study was to evaluate the reliability of the CCT videos that are shared through smartphone in the diagnosis.

Methods: The CCT videos that were sent via WhatsApp were examined in 9 sections: soft tissue, bone structure, parenchyma, ventricle, vascular structures, middle ear, orbits, sinuses and the extra axial space.

Results: The CCT videos were analyzed in 9 sections; there was a perfect agreement among specialists in one of these sections, good agreement in 6 and poor agreement in 2. When compared with the gold standard, it was shown that 5 out of 9 sections could be an alternative to the gold standard.

Conclusions: It may be thought that evaluation of the CCT videos can be obtained with messenger applications such as WhatsApp, which is a cheap, fast and common application. But this study shows that diagnostic images and videos shared through the smartphone by a messenger application can not be an alternative to standard evaluations.

Keywords: WhatsApp, Multidedector Computed Tomography, Video Recording, Smartphone.

Kranial Bilgisayarlı Tomografi Videolarını Değerlendirmek İçin Akıllı Telefon Kullanma: Gözlemciler Arası Çalışma

ÖZET

Amaç: Birçok klinisyen akıllı telefonlarından Beyin Bilgisayarlı Tomografi (BBT) görüntüleri veya videoları ile hasta değerlendirmektedir. Bu çalışmanın amacı, akıllı telefon aracılığıyla paylaşılan BBT videolarının tanıda güvenilirliğini değerlendirmektir.

Gereç ve Yöntem: WhatsApp üzerinden gönderilen BBT videoları 9 bölgeye ayrılarak değerlendirildi: yumuşak doku, kemik yapısı, parankim, ventrikül, damar yapıları, orta kulak, orbita, sinüsler ve ekstra aksiyel alan.

Bulgular: BBT videoları 9 bölümde incelendi; bu bölümlerden birinde uzmanlar arasında mükemmel uyum, 6'sında iyi uyum, 2'sinde zayıf uyum vardı. Altın standart ile karşılaştırıldığında, 9 bölümden 5'inin altın standardına alternatif olabileceği gösterildi.

Sonuç: BBT videolarının değerlendirilmesinin ucuz, hızlı ve yaygın bir uygulama olan WhatsApp gibi mesajlaşma uygulamaları ile sağlanabileceği düşünülebilir. Ancak bu çalışma, bir messenger uygulaması tarafından akıllı telefon üzerinden paylaşılan tanısal görüntü ve videoların standart değerlendirmelere alternatif olamayacağını göstermektedir.

Anahtar Kelimeler: Whatsapp, Çok Kesitli Bilgisayarlı Tomografi, Video Kayıt, Akıllı Telefon.

INTRODUCTION

The use of cranial computed tomography (CCT) has become an important tool in the emergency department (ED), especially in the management of patients with head trauma. The CCT has become the first-choice imaging method in patients with head trauma due to the facts that it provides rapid evaluation, has a low number of contraindications, has high sensitivity and it is easily accessible in our country (1). However, the diagnostic support of clinics such as the emergency medicine, radiology, neurology and neurosurgery are sometimes needed in the evaluation of the CCT images obtained in the ED. This support, both within the hospital itself and among hospitals that are not integrated with each other, is often provided by social media applications such as WhatsApp via smartphones. Evaluating CCT videos on a smartphone is a confusing ethical and technical problem for physicians. Medical assessments via WhatsApp have often been the subject of articles (2-4). The aim of this study was to evaluate the reliability of the CCT videos that are shared via WhatsApp application in the diagnosis.

MATERIAL AND METHODS

The study was initiated with the approval of the Local Ethics Committee. Using the appropriate random sampling method, the CCT scans of the first 111 patients who had presented to the ED starting from the first day of January 2020, which were performed with the appropriate imaging technique, were included in the study. Thirteen radiologists/radiology residents were interviewed for the study. Five radiologists/radiology residents who agreed to participate in the study were quizzed with 20 the CCTs that had not been included in the study and chosen through the hospital's Picture Archiving and Communication System (PACS), the success rate of 2 of which had exceeded 90% were included in the study.

Process

First Step: 111 the CCT scans were first evaluated by two radiologists (one with 20 years and the other with 4 years of experience) on a medical monitor (Totoku brand, 3MP 21.3-inch medical monitor) on a desktop computer. The scans were interpreted in a low-light quiet environment in the radiology evaluation room and the pathologic findings were recorded. These results made with the consensus among the radiologists have been accepted as the gold standard.

Second Step: The CCT scans were recorded on videos with an iPhone 7 plus smart (12 MP camera) phone. The video recording was carried out at a distance of 30 cm in an artificially lit environment without daylight, without using flash and direct light on the computer screen. Each video was short (≤30 seconds), included 90-110 sections (half containing parenchyma, half containing bone window).

Third Step: The smartphone of the participants were tested and calibrated by a multicolor video. These videos (with MP4 extension; with a mean picture frame seconds of 28.98; resolution 480p: 854x480 and about 4.6-5.8 mb) were sent to two different participants via WhatsApp application (one radiologist with 20 years of experience, the other 3.5-year radiology resident) and they were asked to evaluate the videos. The evaluation process was carried out in a closed and illuminated environment without daylight, without direct exposure of light to the phone screen. One radiologist (Mobile1) evaluated the videos with a Samsung Galaxy S6 Edge (5.1 Inch Super AMOLED screen, 1440x2560 (QHD) Pixel resolution), and the other (Mobile2) with an iPhone 6 (4.7-inch IPS 750 x 1334 pixels 326 ppi), and these evaluations were written in the pre-prepared forms. The CCT videos were examined in 9 sections: soft tissue, bone structure, parenchyma, ventricle, vascular structures, middle ear, orbita, sinuses and the extra axial space. If any finding (whether acute, chronic or pathological) were seen or not seen in the relevant sections, it was indicated by the signs "x finding" and "normal". The evaluations made were analyzed as follows:

Statistical Analysis: The agreement between the two participants was examined with the kappa coefficient. The interpretation of agreement accordingly was as follows; a kappa value higher than 0.76: perfect agreement, a kappa value between 0.40-0.75: substantial beyond chance, between 0.00-0.39: poor beyond chance and values lower than zero: no agreement (5). Sensitivity, Specificity, PPV, NPV and Accuracy measurements, as well as the ROC analysis and AUC (areas under the curve) were compared in measuring the adequacy of the diagnoses. As descriptive statistics mean±standard deviation was given for the numerical variables and number and % values were given for the categorical variables. The SPSS Windows version 21.0 package program was used for the statistical analysis and a p value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 52.30±23.47 and 58.6% (n= 65) of the patients were male. The most common complaint on admission was determined to be trauma (40.6%) (Table 1).

Table 1. Descriptive statistics of the patients

Age (mean±sd)	52.30±23.47
Male/Female (%)	65 (58.6) / 46 (41.4)
Reason for presentation (%)	45 (40.6%) traumas 28 (25.2%) neurological deficits 19 (17.1%) dizziness 12 (10.8 %) headaches 7 (6.3%) other

Considering the answers given by the two radiologists while interpreting the CCT videos, the highest success rate was seen in the extra-axial space (Mobile1 & 2: 98.2%), and the lowest success rate was seen in the ventricule analysis (Mobile1: 80.2% & Mobile2: 59.5%) (Table 2).

Table 2. Findings detected on CCTs and the answers of the participants

Evaluated region	*Monitored findings (Gold Standard)*	*Mobile 1*	*Mobile 2*
Soft tissue n (%)	Normal findings 104 (93.7%) Subcutaneous hematoma 2 (1.8%) Soft tissue swelling 5 (4.5%)	Correct answer 98 (72.1%) • Normal 93 (67.6%) • Finding 5 (4.5%) False positive 11 (9.9%) False negative 2 (1.8%)	True answer 96 (86.5%) • Normal 95 (85.6%) • Finding 1(0.9%) False positive 7 (6.3%) False negative 8 (7.2%)
Bone n (%)	Normal findings 104(93.7%) Fracture 5 (1.8%) Craniotomy area 2 (4.5%)	True answer 93 (83.8%) • Normal 88(79.3%) • Finding 5(4.5%) False positive 16 (14.4%) False negative 2 (1.8%)	True answer 98 (88.3%) • Normal 94 (84.7%) • Finding 4 (3.6%) False positive 10 (9%) False negative 3 (2.7%)
Parenchyma n (%)	Normal findings 70(63.1%) Ischemic sequelae 17 (15.3%) Acute/subacute ischemia 7 (6.3%) Hypodense lesion 3 (2.7%) Encephalomalacia 5 (4.5%) Surgical sequelae 1 (0.9%) Atrophy findings 8 (72%)	True answer 88 (79.3%) • Normal 60(54.1%) • Finding 28(25.2%) False positive 15 (13.5%) False negative 8 (7.2%)	True answer 94 (84.7%) • Normal 59(53.2%) • Finding 35(31.5%) False positive 11 (9.9%) False negative 6 (5.4%)
Ventricule n (%)	Normal findings 99 (89.2%) Ventricular enlargement 12 (10.8%)	True answer 89 (80.2%) • Normal 82 (73.9%) • Finding 7 (6.3%) False positive 17 (15.3%) False negative 5 (4.5%)	True answer 66 (59.5%) • Normal 55 (49.6%) • Finding 11 (9.9%) False positive 44 (39.6%) False negative 1 (0.9%)
Vascular n (%)	Normal Findings 102 (91.9%) Calcification 8 (7.2%) Spontaneous Subarachnoid hemorrhage 1 (0.9%)	True answer 99 (89.2%) • Normal 98 (88.3%) • Finding 1 (0.9 %) False positive 4 (3.6%) False negative 8 (7.2 %)	True answer 93 (83.6%) • Normal 88 (79.3%) • Finding 5 (4.5%) False positive 14 (12.6%) False negative 4 (3.6%)
Middle ear n (%)	Normal Findings 110 (99.1%) Effusion 1 (0.9%)	True answer 105 (94.6%) • Normal 105 (94.6%) • Finding 0 (0%) False positive 5 (4.5%) False negative 1 (0.9%)	True answer 106 (95.5%) • Normal 106 (95.5%) • Finding 0 (0%) False positive 4 (3.6%) False negative 1 (0.9%)
Sinus n (%)	Normal Findings 83 (74.9%) Cyst 2 (1.8%) Mucosal thickening 14 (12.6%) Polyp 3 (2.7%) Septal deviation 9 (8.1%)	True answer 91 (82%) • Normal 78 (70.2%) • Finding 13 (11.8%) False positive 5 (4.5%) False negative 15 (13.5%)	True answer 83 (74.8%) • Normal 71(64%) • Finding 12(10.2%) False positive 12 (10.8%) False negative 16 (14.4%)
Orbit n(%)	Normal Findings 111 (100%)	True answer 103 (92.8%) • Normal 103(92.8%) • Finding 0(%) False positive 8 (7.2%) False negative 0 (%)	True answer 108 (97.3%) • Normal 108 (97.3%) • Finding 0(%) False positive 3 (2.7%) False negative 0 (%)
Extra-axial space n (%)	Normal Findings 109 (89.2%) Hemorrhage 1 (9.9%) Menengioma 1 (0.9%)	True answer 109 (98.2%) • Normal 107(96.4%) • Finding 2 (1.8%) False positive 2 (1.8%) False negative 0 (%)	True answer 109 (98.2%) • Normal 107(96.4%) • Finding 2(1.8%) False positive 2 (1.8%) False negative 0 (%)

When the agreement between the two radiologists was examined, perfect agreement was determined for the extra-axial space (Kappa: 1.0; p = 0.001) and a substantial agreement beyond chance (Kappa: 0.40-0.75; p = 0.001) was determined in the evaluation of soft tissue, bone, parenchyma, middle ear, sinuses and the orbita.

In the evaluation of ventricular and vascular structures, a poor agreement was determined between the two participants (Kappa <0.39; p = 0.001) (Table 3).

Table 3. Concordance analysis between the two participants

		Kappa value	P value
Soft tissue	*Mobile 1* / *Mobile 2*	0.723	**0.001**
Bone	*Mobile 1* / *Mobile 2*	0.697	**0.001**
Parenchyma	*Mobile 1* / *Mobile 2*	0.733	**0.001**
Ventricle	*Mobile 1* / *Mobile 2*	0.330	**0.001**
Vascular	*Mobile 1* / *Mobile 2*	0.282	**0.001**
Middle ear	*Mobile 1* / *Mobile 2*	0.421	**0.001**
Sinuses	*Mobile 1* / *Mobile 2*	0.591	**0.001**
Orbit	*Mobile 1* / *Mobile 2*	0.527	**0.001**
Extra-axial space	*Mobile 1* / *Mobile 2*	1.0	**0.001**

Kappa value >0.76 excellent concordance. 0.40-0.75 good concordance. 0.00-0.39 poor concordance (1). Significant p >0.05

A statistically significant agreement was determined between the soft tissue evaluations made by the two specialists on the phone (Kappa=0.723 p=0.001). Similarly, in the bone, parenchyma, ventricle, vascular structures, sinuses, middle ear, orbita and the extra-axial space evaluations, a statistically significant agreement was achieved between the diagnoses made by the two specialists on the phone. The highest level of agreement of the two specialists (Kappa=1) was observed in the extra-axial space assessment, whereas the lowest level of agreement (Kappa=0.282) was determined in the vascular assessment.

Comparing the two radiologists with the gold standard according to Sensitivity, Specificity, PPV, NPV and Accuracy and the AUC values, soft tissue, bone, parenchyma, ventricle and orbital evaluations made through WhatsApp application were found to be sufficiently consistent to be an alternative to the evaluations made on the standard computer screen ($p<0.05$). In the evaluation of the vascular structures, only the evaluations of Mobile 2 participants were consistent, which may be an alternative to the gold standard (Sensitivity: 0.56; Specificity: 0.86). While the evaluations of two radiologists could not be an alternative to the gold standard in the evaluation of sinus structures, orbital and extra-axial structure evaluations could not be evaluated (Table 4).

Table 4. Comparison of the two participants with the gold standard

		Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**	**AUC**	**p**
Soft tissue	*Mobile 1*	0.71	0.89	0.31	0.98	0.88	0.80	**0.007**
	Mobile 2	0.57	0.91	0.31	0.97	0.89	0.74	**0.032**
Bone	*Mobile 1*	0.71	0.85	0.24	0.98	0.84	0.78	**0.013**
	Mobile 2	0.57	0.90	0.29	0.97	0.88	0.73	**0.036**
Parenchyma	*Mobile 1*	0.68	0.86	0.74	0.82	0.79	0.77	**0.001**
	Mobile 2	0.85	0.84	0.76	0.91	0.85	0.85	**0.001**
Ventricle	*Mobile 1*	0.58	0.83	0.29	0.94	0.80	0.71	**0.020**
	Mobile 2	0.92	0.56	0.20	0.98	0.59	0.74	**0.008**
Vascular	*Mobile 1*	0.11	0.96	0.20	0.92	0.89	0.54	0.721
	Mobile 2	0.56	0.86	0.26	0.96	0.84	0.71	**0.038**
Middle ear	*Mobile 1*	0.46	0.94	0.72	0.84	0.82	0.70	**0.001**
	Mobile 2	0.43	0.86	0.50	0.82	0.75	0.64	**0.025**
Sinuses	*Mobile 1*	0.00	0.95	0.00	0.99	0.95	0.47	0.938
	Mobile 2	0.00	0.96	0.00	0.99	0.95	0.48	0.950
Orbit	*Mobile 1*	0.00	0.93	0.00	1.00	0.93	*NC*	
	Mobile 2	0.00	0.97	0.00	1.00	0.97	*NC*	
Extra-axial space	*Mobile 1*	0.00	0.89	0.00	1.00	0.89	*NC*	
	Mobile 2	0.00	0.89	0.00	1.00	0.89	*NC*	

PPV:Positive predictive value. NPV: Negative predictive value. AUC: Area under the curve. NC: Non-calculated. Significant p >0.05

DISCUSSION

There are contradictory results in studies evaluating the photographs of direct radiographies to be sent to the participants vie WhatsApp and similar applications. The decrease in the image quality according to the quality of both the program and the phone used by the participants is an issue to be discussed (3). While these evaluations have been

found to be reliable in some studies, contrary results have been found in some other studies (3,6,7). Evaluation requests made by sharing images (photo or video) with such applications can be requested, especially when there is a need for support from physicians working in hospitals that are not integrated with each other, or in cases where the hospital's PACS system does not have a mobile version. There are also suggestions that sharing tomography videos with the healthcare team in the hospital would enable rapid decision making and rapid treatment planning (8). Radiologists, with whom many images are shared, including the CCT images and videos taken in the emergency or other wards, often evaluate these images and express their opinions. However, how accurate and reliable is the evaluation of these videos sent via WhatsApp? This study was created to discuss this situation.

The consultation process has begun to be standardized in many institutions by sharing radiographs, ECG, skin lesion, laboratory results and sometimes tomography images via WhatsApp. In a survey study conducted with 87 oral medicine and radiology specialists, 95.40% of the specialists were found to evaluate the images consulted with their smart phones with WhatsApp application (9). In the study of Gülaçtı et al., it was found that radiograph sharing was utilized mostly by orthopedic surgeons (2). When the remote consultations with text messages, photos, videos and voice messages sent to the oral medicine and radiology experts via WhatsApp are examined, the evaluations have been shown to give accurate results with a high percentage of 82% (10). As seen from these examples, WhatsApp application can be an alternative to many expensive applications used for telemedicine due to its advantages such as being cheap, accessible and globally used for consultation purposes (11).

The contribution of the application to the consultations has been widely discussed in the literature (2,10,12). Handelman et al. had the PA chest radiographs sent on the WhatsApp app interpreted by 12 interns, and their interpretations were then compared with the comments of radiologists who interpreted the radiographs on the computer screen. In this study, no significant difference was found between the two groups (3). Another study that we would like to mention is the inter-observer study of Şener et al. with urologists, because it has a similar concept, although it did not include radiological imaging. In the study, it was shown that the sensitivity and specificity of spot urine sample photographs sent via WhatsApp were high in determining the presence and severity of hematuria (13). In the intra-observer study made by Stahl et al. with thoracolumbar CT videos sent to orthopedic surgeons via WhatsApp, it was shown to have a very good agreement with fracture, calcification, follow-up of treatment, neural canal penetration and evaluation of the Denis classification (14). In another study carried out by Stahl et al. by sending the X-ray images taken due to orthopedic traumas in children via WhatsApp application, they found an almost perfect agreement between WhatsApp reviews and the standard computer screen reviews (15).

Issues such as the change of image quality during transfer, the fact that the images are not evaluated by a user on a standard phone (not every user uses the same phone), the amount of light in the indoor and outdoor environment may affect the evaluation and which images can be effectively evaluated this way, are still not clarified. In our study that the CCT videos were analyzed in 9 sections, there was a perfect agreement among specialists in only one of these section, good agreement in 6 and poor agreement in 2. When compared with the gold standard, it was shown that 5 out of 9 sections could be an alternative to the gold standard. However, sensitivity (11-92%) and specificity (56-97%) vary according to the section and user. In addition, although the correction rate is high in the comments made by the participants (59.5-98.2%), false positivity (1.8-39.6%) and false negativity (0-14.4%) also show serious variation. When we consider CCT as a whole, it is not appropriate to use this method in almost all of the sections we determined because of low sensitivity. Therefore, using smartphone and messenger applications could not be alternative to evaluate of the CCT.

The CCT is one of the most frequently used examination techniques in emergency departments. Low cost, ease of accessibility and being a method that provides fast results are among the reasons for this method being preferred (1). Trauma-related injuries are among the most common reasons for presentation to ED. In our study, 40.6% of the patients who had undergone CCT had presented to the ED due to trauma. In the study of Yıldız et al., 42.9% of the patients who had undergone CCT had similarly presented with trauma (1). In another study conducted in our country, 46.8% of patients who had undergone CCT had a traumatic etiology (16) Due to the high mortality of intracranial injuries caused by severe head trauma (10-40%), we think that the CCT will continue its popularity in the emergency departments as it is an effective method in the early diagnosis of lesions associated with trauma (1,17).

Although the numbers of the CCT scans are gradually increasing due to its rapid and inexpensive nature, the detected intracranial pathology rates are quite low. Positive CCT findings were observed in 159 (4.1%) of 3866 patients in the study of Osmond et al, 24 of whom (0.6%) had undergone neurosurgical operations (18). Yıldız et al. retrospectively examined the CCT images of 1700 patients, and 1427 (83.94%) of these patients did not have any acute pathology in

their CCT images (1). In 42 (37.8%) of 111 CCT videos included in our study, no pathology was observed in any area. Acute pathology was observed in 14 (12.6%) cases (skull fracture in 5 (4.5%) cases, acute/subacute ischemia in 7 (6.3%) cases, subarachnoid hemorrhage in 1 (0.9%) case and extra-axial bleeding in 1 (0.9%) case)). The high levels of normal CCT scans may be attributed to the increased defensive medicine approaches due to different reasons (such as severity, malpractice, pressure by the patient and their relatives', insufficient follow-up area).

CONCLUSION

It may be thought that evaluation of the CCT videos can be obtained with messenger applications such as WhatsApp, which is a cheap, fast and common application. But this study shows that diagnostic images and videos shared through the smartphone by a messenger application can not be an alternative to standard evaluations. It is more appropriate to use FDA-approved Digital Imaging and Communications in Medicine (DICOM) viewers applications rather than using social media applications (19-21). However, it is recommended to use these applications in emergency situations rather than primary diagnostic evaluation and to repeat the evaluation on the standard monitor as soon as possible (22,23).

Ethics Declarations

Declaration of Conflicting Interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Informed Consent: The informed consent was obtained from each participants.

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RESEARCH ARTICLE

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A Field Study on Determining the Social Media Addiction Levels of Academicians: Validity and Reliability Study

ABSTRACT

Objective: The main purpose of this research was to find out the social media addiction levels of academicians and to reveal whether the scale used is a valid and reliable scale. In addition, it is another aim of the study to determine which variables differ in terms of social media addictions of academics whose social media addiction levels are determined.

Methods: A total of 430 academicians, 199 of whom were females and 231 males, participated in this study. The validity and reliability of the scale were tested by performing exploratory and confirmatory factor analyzes and reliability analyzes on the data collected from the academicians reached by the online survey method. Then, the differences of the factors, whose validity and reliability were ensured by using parametric techniques, according to demographic variables were examined.

Results: The exploratory factor analysis done on the data collected from academicians reached by online survey method, showed that the scale had four sub-factors called Virtual Tolerance (Slacking), Virtual Interaction, Virtual Communication, and Emotional State. Obtained sub-factors were subjected to confirmatory factor analysis and it was seen that the fit indices gave good results. Since the Cronbach's alpha value, which was used to measure the reliability of the scale, was also high, the scale used to measure the social media addiction levels of academicians was found to be valid and reliable. The differences of the factors that were found to be valid and reliable according to demographic variables were examined.

Conclusions: The result of the analysis demonstrated that addiction levels of single academicians were more than that of the married academicians; young or old academicians' social media addiction levels were more than that of middle-aged academicians. Clearly, this study revealed that as the academic title increases, social media addiction levels of academicians decreases.

Keywords: Virtual Tolerance-Interaction and Communication, Social Media Addiction, Exploratory and Confirmatory Factor Analysis, Reliability, Statistical Analysis.

Akademisyenlerin Sosyal Medya Bağımlılık Düzeylerinin Belirlenmesine Yönelik Bir Saha Araştırması: Geçerlilik ve Güvenilirlik Çalışması

ÖZET

Amaç: Bu araştırmanın temel amacı akademisyenlerin sosyal medya bağımlılık düzeylerini ortaya çıkarmak ve kullanılan ölçeğin geçerli ve güvenilir bir ölçek olup olmadığını ortaya koymaktır. Ayrıca sosyal medya bağımlılık düzeyleri belirlenen akademisyenlerin bu bağımlılıklar açısından hangi değişkenlerin farklılaştığını belirlemek de çalışmanın bir diğer amacıdır.

Gereç ve Yöntem: 199'u kadın, 231'i erkek olmak üzere toplam 430 akademisyen bu çalışmaya katılmıştır. Çevrimiçi anket yöntemiyle ulaşılan akademisyenlerden toplanan veriler üzerinde açımlayıcı ve doğrulayıcı faktör analizleri ile güvenirlik analizleri yapılarak ölçeğin geçerliliği ve güvenirliği test edilmiştir. Daha sonra parametrik teknikler kullanılarak geçerliği ve güvenirliği sağlanan faktörlerin demografik değişkenlere göre farklılığı incelenmiştir.

Bulgular: Yapılan açımlayıcı faktör analizi, ölçeğin Sanal Tolerans (Gevşeme), Sanal Etkileşim, Sanal İletişim ve Duygusal Durum olmak üzere dört alt faktöre sahip olduğunu göstermiştir. Elde edilen alt faktörler doğrulayıcı faktör analizine tabi tutulmuş ve uyum indislerinin iyi sonuçlar verdiği görülmüştür. Ölçeğin güvenirliğini ölçmek amacıyla yapılan cronbach's alfa değeri de yüksek çıktığı için akademisyenlerin sosyal medya bağımlılık düzeylerini ölçmek için kullanılan ölçek geçerli ve güvenilir bulunmuştur. Geçerliği ve güvenirliği sağlanan faktörlerin demografik değişkenlere göre farklılığı incelenmiştir.

Sonuç: Bekâr akademisyenlerin bağımlılık düzeylerinin evli akademisyenlere göre daha fazla olduğu; genç ve yaşlı akademisyenlerin sosyal medya bağımlılık düzeylerinin ise orta yaşlı akademisyenlere göre daha fazla olduğu ortaya çıkmıştır. Yapılan bu araştırmada ayrıca akademik unvan arttıkça akademisyenlerin sosyal medya bağımlılık düzeylerinin de düştüğü ortaya konulmuştur.

Anahtar Kelimeler: Sanal Tolerans-Etkileşim ve İletişim, Sosyal Medya Bağımlılığı, Açımlayıcı ve Doğrulayıcı Faktör Analizi, Güvenilirlik, İstatistiksel Analiz

INTRODUCTION

We left behind a period in which we learned about the developments in the world from the mass media and moved to a new era where we are learning the same developments from people through social networks. Recently, when the global village is completely networked, the amount of information we can reach, and deliver has increased considerably thanks to new communication technologies that are getting cheaper and widespread. We could not even imagine a life without new communication technologies integrated into smartphones in the age we live in, where access to information is easier than ever.

However, human beings have become free with the comfort of being able to reach anywhere in the world with a single button and express their ideas without limits. This rapid life produces a great paradox for humans. The posts shared on interactive internet environments, called social media, have revealed some people living their private or professional lives publicly. While some have come to the fore with their posts, others have begun to follow shared lives. Thus, an unhappy person of modern life has started a new and unknown journey to an alternative happy life. People seem to satisfy all kinds of expectations in virtual lives, and this virtual satisfaction has become more and more attractive day after day. Day by day, the interest in social networks has become more than a habit and started to be accepted at the level of "addiction".

Many studies on social media addiction in social sciences have just begun and still been done in virtual field. In virtual areas where users create and present their profiles, these profiles vary according to some interest areas such as hobby, profession, likes, etc. (1). As the time elapsed in these networks, which include people of all ages and professions, the element of curiosity about the effects and motivations of these networks has increased. In this context, the relationship between social media and addiction has been examined in different sample groups. For instance, Sümen and Evgin's study examines the relationship of high school students' social media addiction with sleep quality and psychological problems (2). As a result of the research conducted with 1274 students, it was determined that the young people included in the sample could not sleep efficiently and their sleep quality was low. The study, which was conducted in a different sample group, was conducted with 329 undergraduate students in Afghanistan. As a result of the study, it was revealed that there is a positive relationship between social media, addiction and depression (3). At the same time, attitudes and addiction levels are tried to be determined in these studies by considering the demographic variables.

Given the relationship between social media and addiction, one should examine the impact of internet, which we can define as an inevitable desire for an object or asset. This is because one cannot talk about social media without internet. Healthy internet use is defined as using the internet for a certain purpose and without a cognitive or behavioral disturbance in a reasonable amount of time (4). The cheap and easy accessibility of the internet, the possibility of people of all ages and socio-economic levels to access the internet have caused people to develop different behavioral patterns that attract attention and are suitable for examination. Based on this, research being conducted in recent years have focused on the internet, social media, and addiction behaviors (5).

In addition to the research being made especially on young people, it has begun to wonder how the other part of the society also uses social media. Thereupon, studies are conducted with various age groups and professional groups on the relationship between social media and addiction. In a study investigating the effect of social media addiction on the level of depression in adults, it was determined that working individuals spend less time on social media than students or job seekers. However, as the duration of social media use increases, it has emerged that social media addiction and depression increase (6). In a study measuring the social media usage practices of 16 people aged 60-80 in Singapore found that "social media apps' use among participants was moderated by personal attitudes and social influences. Second, participants perceived social media apps' use as both positive and negative influences on health-related outcomes" (7). This study aimed to determine the relationship between social media and the addiction of academicians who have scientific autonomy and a public legal personality and who are responsible for providing education in institutions where high-level education and training are provided. It is of great importance in revealing the social media addiction levels of the academicians who direct the young part of the society.

Social Media and Addiction Relationship: Regardless of generation, social media has become an important part of people of all ages and one of the most discussed topics in every part of society. The ability to present many features such as entertainment, information, communication, game, and hobby to people at the same time makes social media even more attractive. Besides, communication technologies have become smaller and integrated with

technologies have become smaller and integrated with new technologies and have more features, strengthening mobile communication and

expanding the use of social media. Moreover, mankind has started to spend more time on social media, which has become a part of the most important daily habits.

Boyd and Ellison have described that social networks among social media are at the center of almost everyone as, "web-based services that allow individuals to create an open or semi-open profile in a limited system, allowing them to view and follow the contact lists created by themselves or other users within the system, as well as to list their profiles" (8). These networks, which include various elements such as interaction, content creation, and entertainment, have become popular with their ability to meet every need. The definitions of social networking sites are mostly about 'interaction'. Koh et al. describe social network sites as "users interact with real-life friends and meet other people with common interests in these web-based virtual communities"; they also describe social networks as one of the greatest pushing forces behind internet users (9).

Social media has begun to be considered a new type of addiction in medical literature as it has become one of the basic habits of humankind. This new addiction type is called "social media addiction", evaluated as one of the most important syndromes of the modern era and it is claimed that this addiction has increased especially with the spread of smartphones (10).

Addiction is defined as "being addicted, dependency" according to the Turkish Language Association, and addicted is defined as "depending on the will, power and help of something else, without freedom, autonomy" and "the people who are materially or spiritually overly attached to a person or thing" (11). In this context, addiction is deterioration in behavioral control and a condition that causes significant problems with craving, a person's behavior, and relationship with people. Addiction, like other chronic diseases, often reoccurs (12).

People have become more addicted to social media that can be used at any time and in any place. The research about social media has shown that especially young people are "addicted" to social networking sites; however, the effects of this "addiction" have not been fully identified yet (13). Some scholars have found that individuals with emotional and psychological disorders have a higher tendency to be addicted to online activities to meet their social and emotional needs as doing these activities on social networking sites is easy and anonymous (9). One of the most significant characteristics of social media addiction is spending a great deal of time on these sites. Some studies on this topic have shown that the amount of time spent in social media is related to interaction in real-life communities less (14).

Addiction, having an important potential for unwanted harmful things, is obtained as a result of engaging in this behavior, is considered as a repetitive strong motivation to perform a deliberate behavior without survival value (12), when combined with social media. Considering the innovation of this technology, addiction can cover a wide variety of issues. For instance, according to Maslow's hierarchy of needs, people's necessities are in five stages (15). The first two of these are physiological needs such as eating and drinking and the need for safety. In the third stage, a state of affection and belonging takes place. After the need for respect is met, the last step, the need for self-realization appears (15). Riva et al. in their work named "Psychology of Social Media: From Technology to Identity" having been held in 2015, investigated which of Maslow's five-stage needs falls under the need to use social networks. Some researchers have suggested that social networks help to meet the needs of their users in the following categories (1):

(i) Security requirements: People can choose who to communicate with, control what they say about themselves, and comment. On some social media networks such as Facebook, users can categorize their friends as close friends or just friends as there are some privacy settings to arrange this. Doing this makes people feel safe.

(ii) Relational needs: Users can exchange ideas with "friends" on social networks and share source applications. They can even search for a soulmate if necessary. Today, we can meet and communicate with some people whom we do not know and have never seen before. Looking at the profiles on Facebook, it is seen that there are people who have many friends that they cannot meet in real life.

(iii) The need for being loved and belonged: People can choose their "friends" on social networks. Therefore, if someone chooses to be a "friend" then "that person is worth it". People feel valuable with the numbers of their followers and friends on Facebook and Instagram. The more followers and friends they have on these kinds of social network sites, the more valuable they feel themselves.

(iv) The need for self-realization: A person can show himself or herself (who he/she is and what he/she does) as he/she wishes and transfers his/her abilities to some "friends". Another area where social media users meet their needs for self-realization is YouTube. YouTube, a social network that allows content sharing individuals' desire to spy and be seen (16) also freely shares the content produced by people and offers them to their "friends". This feature of YouTube suits the self-realization need in terms of showing oneself and his abilities.

The researchers have studied the relationship between social media and addiction on different sample groups and variables. Especially young people mostly use some new communication technologies and social media; therefore, social media can be the subject of research mainly on this age group. Research done in the USA found that there were some psychosocial factors in the relationship between university students and young adults and social media. Scholars have found that one of these factors was loneliness and first-year university students in the USA used social networks to connect and meet (9). In this sense, "friends" in social networks have become as close as a network when needed.

Social media platforms (Facebook, Twitter, Instagram, YouTube, etc.) are used to fulfill the necessity to communicate in daily life. Social media can sometimes be related to people's professions. Almost every profession has started running their business from online networks. For example, politicians have tended to make their announcements on Twitter; therefore, journalists have begun to use those social networks as a source. Apart from these, even ordinary citizens cannot stay away from social media and new internet-based illnesses have taken place in the literature (17).

Using more than needed, difficulty in stopping, and neglecting other activities are some of the symptoms used to describe social media addiction (14). Spending a lot of time on social networking sites is one of the most apparent features of social media addiction. The experts have developed different scales and tried to determine the state of social media addiction with different sample groups.

MATERIAL AND METHODS

Dataset: The sample of this research consists of 430 academicians with an average age of 35.31±7.42, 231 (53.7%) female and 199 (46.3%) male individuals.

Instruments: In the present study, the "Social Media Addiction Scale-Adult Forum (SMAS-AF)", developed by Şahin and Yağcı, was used to measure the social media addiction levels of academicians (18). This scale had a five-point Likert-type scale, consisting of 18 items. SPSS 22.0 program was used in the evaluation and the statistical significance limit was accepted as $p<0,05$.

Two reversed items of the 20-item scale were not included in the present study. Unlike Şahin and Yağcı, this study examined whether there was a statistically significant difference in terms of demographic variables in terms of the overall and sub-factors of the scale together with validity-reliability analysis.

Sahin and Yagci also applied exploratory factor analysis on the 20-item SMAS-AF scale they developed, and they obtained a 2-factor structure. In the present study, a 4-factor structure emerged as a result of the exploratory factor analysis of the 18 items used in the scale.

Descriptive Statistics of the Participants: The frequency values of the academicians participating in the present research according to their gender, age, marital status, and academic title were given in Table 1.

Table 1. Descriptive Statistics of Academicians Participating in The Research

		Frequency (N)	Percent (%)	Cumulative Percentage (Σ%)
Gender	Female	231	53.7	53.7
	Male	199	46.3	100.0
	Total	430	100.0	
Age	Between 20-29	85	19.8	19.8
	Between 30-39	242	56.3	76.0
	Between 40-49	86	20.0	96.0
	50 and 50^{+}	17	4	100.0
	Total	430	100.0	
Marital Status	Single	167	38.8	38.8
	Married	263	61.2	100.0
	Total	430	100.0	
Academic Title	Research Assistant	139	32.3	32.3
	Instructor	115	26.7	59.1
	Assis. Prof.	122	28.4	87.4
	Asso. Prof.	30	7.0	94.4
	Professor	24	5.6	100.0
	Total	430	100.0	

Of the 430 academicians participating in the study, 231 (53.7%) were female and 199 (46.3%) were male. At the same time, 85 (19.8%) of the participants were in the 20-29 age group, 242 (56.3%) were in the 30-39 age group, 86 (20%) were in the 40-49 age group and 17 of them (4%) were in the age group of 50 and over.

Concerning their marital status, 167 of them (38.8%) were single and 263 (61.2%) of them were married. Concerning the academic titles of the participants, 139 (32.3%) of them were research assistants, 115 (26.7%) of them were lecturers, 122 (28.4%) of them were assistant professors, 30 (%7)

of them were associate professors and 24 (%5.6) of them were professors.

VALIDITY AND RELIABILITY ANALYSIS OF THE SCALE

Validity Analysis

Findings of exploratory factor analysis: In order to reveal the validity of the scale, exploratory factor analysis was performed.

The KMO coefficient of the Kaiser-Meyer-Olkin (KMO) test, having been conducted to determine whether the sample size used in the study was 0.907, showed that the sample size in the study was sufficient. The significance value (p-value) obtained as a result of the Bartlett Test (Bartlett Test of Sphericity) was less than 0.05 ($p < 0.05$), the data provides the assumption of multiple normal distributions (19,20) and thus confirmed the feasibility of factor analysis. In other words, since the Bartlett test was significant, it would be possible to say that there were high correlations between variables (21); therefore, the data set was suitable for factor analysis.

As stated in the method part of the study, Şahin and Yağcı applied exploratory factor analysis to the 20-item SMAS-AF scale they developed and obtained a 2-factor structure. In the present study, a 4-factor structure emerged as a result of the exploratory factor analysis of 18 items used in the scale.

Table 2. Explanatory factor analysis, reliability analysis and descriptive statistics of the scale

Factors:	Variables	$\bar{X}$±SS	Faktor Loads	Explained Variance	Cronbach's Alpha
First Factor:	1.I sometimes slack off my work because I spend too much time on social media.	3.92±1.25	.810	17.994	0.844
	2.I realize that my productivity decreases because of social media.	3.15±1.24	.810		
	3.I spend more time on social media than I plan.	3.39±1.25	.603		
	4.I sometimes neglect my family members because of social media.	3.28±1.14	.567		
	5.I cannot stay away from social media to be informed about current events.	3.10±1.14	.553		
	6.The people around me criticizes me as I spend too much time on social media.	3.39±1.25	.508		
	7.The first thing I do when I wake up is to check social media.	3.75±1.09	.493		
Second Factor:	8.My desire to be aware of the things about various social awareness activities fast makes me use social media more.	2.89±1.31	.782	15.482	0.760
	9.I spend more time on social media to see and share some special announcements.	3.31±1.25	.722		
	10.I cannot stop using social media to take part in humanitarian social projects.	3.22±1.24	.669		
	11.I use social media more to be in touch with social media groups.	2.66±1.36	.641		
Third Factor:	12.I prefer social media friendships to real life friendships.	3.24±1.36	.785	14.153	0.721
	13.I get angry when someone disturbs me while I am using social media.	3.15±1.24	.644		
	14.I express myself better to the people whom I connect on social media.	3.57±1.18	.610		
	15.I prefer to spend time on social media even if there are people around me.	3.75±1.09	.442		
Fourth Factor:	16.I see social media as an escape from real life.	2.91±1.20	.773	12.418	0.690
	17.Being on social media relaxes me when I feel upset.	3.79±1.06	.754		
	18.I feel free when I am on social media.	3.01±1.28	.585		
Evaluation Criteria	Kaiser-Meyer-Olkin Measure of Sampling Adequacy: .907 Barlett's Test of Sphericity; Approx. Chi-Square: 3003.763 Sig. : 0.000 Extraction Method: Principal Components Rotation Method: Varimax Explained Variance Total: 60.047 Cronbach's Alpha: 0.895				

As can be seen in Table 2, the exploratory factor analysis results of the scale indicated that there were 4 factors with an eigenvalue greater than 1. The variance explained by the first factor was found to be 17.994; the variance explained by the second factor was found to be 15.482; the variance explained by the third factor was found to be 14.153 and the variance explained by the fourth factor was found to be 12.418. The total variance explained was found to be 60.047%.

For the confirmatory factor analysis to be applied, there should be at least three variables that measure each latent variable. For this reason, attention was paid to have at least three variables under any factor. In addition, the factor weight should be ± 0.30 and above (21). In the analysis results obtained shown in Table 2, the scale had good construct validity.

Naming the factors. Since the main reason for the exploratory factor analysis is to reduce many variables to a smaller number of factors, these factors must be named. They were named according to the common features of the variables used in the factor (22).

Table 3. Naming the Factors Obtained from Exploratory Factor Analysis (AFA) Scale

Clause No:	Factors:
	First Factor: Virtual Tolerance (Slacking)
S1	I sometimes slack off my work because I spend too much time on social media.
S2	I realize that my productivity decreases because of social media.
S3	I spend more time on social media than I plan.
S4	I sometimes neglect my family members because of social media.
S5	I cannot stay away from social media to be informed about current events.
S6	The people around me criticizes me because I spend too much time on social media.
S7	The first thing I do when I wake up is to check social media.
	Second Factor: Virtual Interaction
S8	My desire to be aware of the things about various social awareness activities fast makes me use social media more.
S9	I spend more time on social media to see and share some special announcements.
S10	I cannot desist from using social media to take part in humanistic social projects.
S11	I use social media more to be in touch with social media groups.
	Third Factor: Virtual Communication
S12	I prefer social media friendships to real life friendships.
S13	I get angry when someone disturbs me while I am using social media.
S14	I express myself better to the people whom I connect on social media.
S15	I prefer to spend time on social media even if there are people around me.
	Fourth Factor: Emotional State
S16	I see social media as an escape from real life.
S17	Being on social media relaxes me when I feel upset.
S18	I feel free when I am on social media.

The items belonging to factors obtained from exploratory factor analysis and their proper names were shown in Table 3. The first factor consisted of 7 items and was named "*Virtual Tolerance (Slacking)*"; the second factor consisted of 4 items and was named as "*Virtual Interaction*"; the third factor consisted of 4 items and was named as "*Virtual Communication*" and the fourth factor consisted of 3 items and was named as "*Emotional State Factor*".

Confirmatory Factor Analysis. To test the correctness and adaptation of the 4-factored structure as a result of exploratory factor analysis, confirmatory factor analysis was performed via the AMOS package program. The first factor "Virtual Tolerance (Slacking)" was coded as F1, the second factor "Virtual Interaction" was coded as F2, the third-factor "Virtual Communication" was coded as F3, and the fourth factor "Emotional State" was coded as F4, during the analysis.

Common values for model fit (model fit) were χ^2/df, GFI, CFI, and RMSEA. In some of the studies, the IFI, RMR, NFI and AGFI values were also examined; however, there was no limit to the values to be looked at. The reported values can change according to the values the researcher wants to draw attention to (23). The fit values for the model created were given in Table 4 and Table 5.

Standardized RMR was = .0629 χ^2/df=3.708≤5 0.85≤GFI=0.885 SRMR=0.0629≤0.08 and RMSEA=0.079≤0.08 according to these fit values, the first level multi-factor model fit the data.

Table 4. Values Obtained from DFA Results

Model	NPAR	CMIN	DF	P	CMIN/DF	RMR	GFI	AGFI	PGFI
Default model	46	463.463	125	.000	3.708	.084	.885	.843	.647
Saturated model	171	.000	0			.000	1.000		
Independence model	18	3052.383	153	.000	19.950	.450	.338	.261	.303

Table 5. RMSEA Values Obtained from DFA Results

Model	RMSEA	LO 90	HI 90	PCLOSE
Default model	.079	.072	.087	.000
Independence model	.210	.204	.217	.000

Estimates output gives the results of the relationships between variables in the analysis. Regression, standardized regression, variance, correlation values, and whether these values were statistically significant were determined.

Regression weights and standardized regression weights showed the regression coefficients. Standardized regression coefficients have been used in interpretation.

Regression weights were given below in Table 6. Regression values show the power of the observed variables to predict hidden variables, that is, factor loadings. Factor loadings are important since the "p" values are less than 0.001 for each pairwise relationship below. The significant factor loadings showed that the items were loaded correctly on the factors. The three-star (***) showed that the p value was less than 0.001.

Table 6. Estimates and Standardized Estimates

			Estimate	S.E.	C.R.	P	Standardized Estimates
S7	<---	F1	1.000				.624
S6	<---	F1	.866	.085	10.155	***	.624
S5	<---	F1	.865	.082	10.570	***	.602
S4	<---	F1	.852	.074	11.452	***	.687
S3	<---	F1	1.145	.094	12.231	***	.749
S2	<---	F1	.979	.094	10.457	***	.597
S1	<---	F1	1.119	.091	12.283	***	.734
S11	<---	F2	1.000				.664
S10	<---	F2	.912	.086	10.555	***	.634
S9	<---	F2	.979	.092	10.638	***	.640
S8	<---	F2	1.163	.100	11.589	***	.727
S15	<---	F3	1.000				.735
S14	<---	F3	.904	.078	11.566	***	.635
S13	<---	F3	.759	.079	9.551	***	.517
S12	<---	F3	.537	.059	9.135	***	.499
S18	<---	F4	1.000				.626
S17	<---	F4	1.219	.113	10.768	***	.737
S16	<---	F4	.911	.095	9.539	***	.600

In addition, the standardized regression weights (standardized regression coefficients) regression coefficients were quite high given in Table 6.

In addition, covariance, correlation and variance values were given in Table 7 and Table 8. All covariance, correlation and variance values were statistically significant since the p values of covariance, correlation and variance values were also less than 0.01.

The diagram of the suitable model obtained by confirmatory factor analysis was given in Figure 1.

Table 7. Estimates for Covariance and Correlations

			(Covariance) Estimate	S.E.	C.R.	P	*(Correlations)* Estimate
F1	<-->	F2	.395	.054	7.295	***	.612
F1	<-->	F3	.537	.062	8.677	***	.822
F1	<-->	F4	.463	.060	7.675	***	.748
F2	<-->	F3	.433	.055	7.930	***	.695
F2	<-->	F4	.326	.050	6.514	***	.553
F3	<-->	F4	.449	.057	7.905	***	.751
e6	<-->	e7	.409	.056	7.255	***	.442
e4	<-->	e5	-.219	.037	-5.877	***	-.354
e1	<-->	e2	-.141	.049	-2.881	.004	-.154
e13	<-->	e15	.184	.038	4.812	***	.284

Table 8. *Variances: (Group number 1 - Default model)*

	Estimate	S.E.	C.R.	P
F1	.678	.100	6.791	***
F2	.614	.089	6.929	***
F3	.631	.080	7.878	***
F4	.565	.089	6.340	***
e1	1.064	.080	13.323	***
e2	.796	.060	13.320	***
e3	.891	.065	13.602	***
e4	.551	.045	12.289	***
e5	.697	.061	11.477	***
e6	1.172	.087	13.527	***
e7	.728	.059	12.434	***
e8	.779	.067	11.656	***
e9	.762	.063	12.112	***
e10	.847	.070	12.020	***
e11	.743	.071	10.390	***
e12	.538	.052	10.268	***
e13	.765	.063	12.221	***
e14	.999	.074	13.430	***
e15	.547	.041	13.393	***
e16	.879	.074	11.926	***
e17	.707	.075	9.476	***
e18	.835	.068	12.285	***

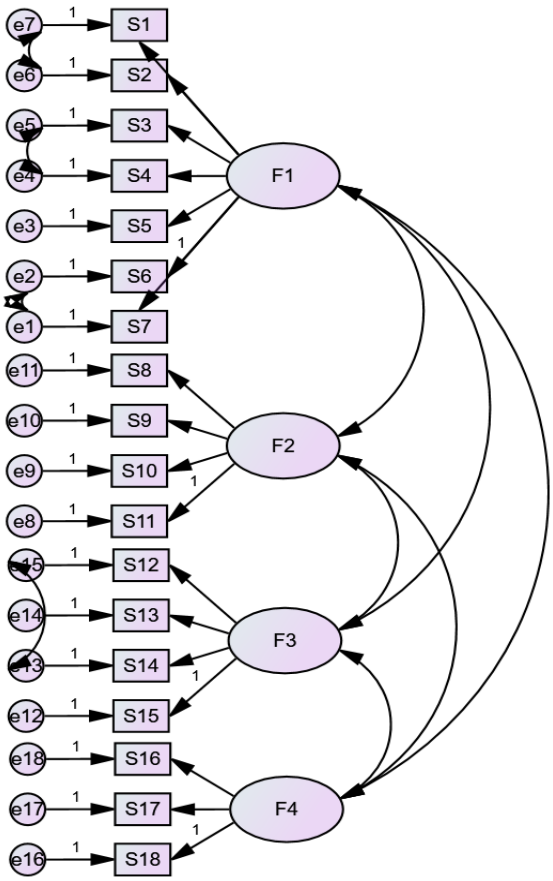

Figure 1. Confirmatory Factor Analysis (CFA)

Reliability Analysis: Reliability analysis was performed in terms of both overall and sub-factors of the 18-item scale directed to the participants, and the internal consistency coefficient (Cronbach's Alpha coefficient) was 0.895 for the overall scale and 0.844 for the Virtual Tolerance, the first factor given in Table 2.

Since the coefficient value obtained in terms of the total and first factor of the scale was higher than 0.80, the scale used was highly reliable (21). The internal consistency coefficients (Cronbach's Alpha coefficient) obtained for the second, third and fourth sub-factors of the scale also showed that they had sufficient reliability given in Table 2.

RESULTS

Examining the Differences of Social Media Addiction According to Demographic Variables: The hypotheses established to examine the difference of social media addiction according to demographic variables are as follows:

H_1: Social media addiction among academicians differs according to gender.

H_2: Social media addiction among academicians differs according to marital status.

H_3: Social media addiction among academicians differs according to age.

H_4: Social media addiction among academicians differs according to academic title.

In order to test the hypotheses, the t-test for independent variables with two categories and the F-test (ANOVA) for independent variables with more than two categories were used.

Analyzing the Differences of Social Media Addiction among Academicians According to Gender: To determine whether social media addiction among academicians differed according to gender, an independent sample t-test was conducted as two categories were belonging to gender.

Table 9. Mean Scores of the Social Media Addiction Level Among Academicians by Gender (Independent Samples Test)

	Gender	N	Mean	Std. Deviation	Sig. (p-value)
General Addiction	Female	231	2.3992	.72520	0.446
	Male	199	2.3470	.68722	
Virtual Tolerance (Slacking)	Female	231	2.4997	.90644	0.399
	Male	199	2.4279	.84899	
Virtual Interaction	Female	231	2.6742	.92619	0.834
	Male	199	2.6558	.89130	
Virtual Communication	Female	231	1.8680	.83366	0.726
	Male	199	1.8945	.73136	
Emotional State	Female	231	2.5065	.93604	0.086
	Male	199	2.3501	.94325	

When the p values obtained as a result of the t-test (equality of the means) were examined, as can be seen in Table 9, the social media addiction level of the academicians did not show a significant difference according to gender in terms of both total addiction and its sub-factors. However, Koh et al. concluded that gender was an important determinant of online social network addiction in the USA. In the same study, female academicians were more likely to become addicted after controlling for demographic and psychosocial factors (9).

In Sinan Aslan's master's thesis titled "Evaluating the Relationship Between Internet Addiction Levels and Health Problems that May Occur" prepared in 2011, it was found that male lecturers use the internet more than females (24). Similarly, a study done by Gezer and Sevim included interviews with 225 teachers in the 2004-2005 academic year (25). In the study, there was a difference in internet use based on gender. Male teachers use the internet 7 % more than females.

As can be seen in Table 9, in the present study, when the average values of social media addiction levels of academicians were examined in terms of gender, the addiction level of female academicians was higher than that of males in other sub-factors except the Virtual Communication and in the overall scale. Despite all the results, although this difference was not statistically significant, the increase in women's internet use was remarkable.

Analyzing the Differences of Social Media Addiction among Academicians According to Marital Status: To determine whether social media addiction among academicians differed according to marital status, an independent sample t-test was conducted.

Table 10. Mean Scores of Social Media Addiction Level Among Academicians by Marital Status (Independent Samples Test)

	Marital Status	N	Mean	Std. Deviation	Sig. (p-value)
General Addiction	Single	167	2.5010	.78146	**0.005**
	Married	263	2.2951	.64517	
Virtual Tolerance (Slacking)	Single	167	2.6322	.94922	**0.003**
	Married	263	2.3612	.81768	
Virtual Interaction	Single	167	2.7545	.92914	0.107
	Married	263	2.6093	.89351	
Virtual Communication	Single	167	1.9671	.88433	0.068
	Married	263	1.8251	.71504	
Emotional State	Single	167	2.5689	1.00821	**0.018**
	Married	263	2.3485	.88802	

As can be seen in Table 10, when the p-values obtained as a result of the t-test (equality of means) were examined, the social media addiction level of the academicians did not differ according to marital status in terms of Virtual Interaction and Virtual Communication sub-factors. However, there was a significant difference according to marital status in terms of General Dependence, Virtual Tolerance (Slacking) and Emotional State sub-factors.

As can be seen in Table 10, when the average values of the social media addiction levels of the academicians were examined in terms of marital status, the addiction level of singles was found to be higher than the married ones in both the overall (total addiction) and sub-dimensions of the scale. However, the difference in Virtual Interaction and Virtual Communication dimensions was not statistically significant. The effect of marital status on addiction was observed when the addiction level was examined in singles where Virtual Loafing and Emotional State sub-factors differed significantly.

Analyzing the Differences of Social Media Addiction among Academicians According to Age: To determine whether social media addiction among academicians differed according to age, the F-test (ANOVA) was conducted because there were more than two categories of age.

Table 11. Mean Scores of Social Media Addiction Level Among Academicians by Age (ANOVA)

	(I) Age	N	Mean	Std. Deviation	F	Sig.	(J) Age	Mean Difference (I-J)	Sig.
General Addiction	**Between 20-29**	85	**2.57**	0.80	5.072	**.002**	**Between 40-49**	**0.41**	**.001**
	Between 30-39	242	2.38	0.67					
	Between 40-49	86	**2.16**	0.70					
	50 and 50^{+}	17	2.47	0.44					
	Total	430	2.38	0.71					
Virtual Tolerance (Slacking)	**Between 20-29**	85	**2.74**	0.98	5.436	**.001**	**Between 40-49**	**0.53**	**.000**
	Between 30-39	242	2.47	0.85					
	Between 40-49	86	**2.21**	0.85					
	50 and 50^{+}	17	2.35	0.59					
	Total	430	2.47	0.88					
Virtual Interaction	**Between 20-29**	85	**2.88**	0.91	3.846	**.010**	**Between 40-49**	**0.44**	**.008**
	Between 30-39	242	2.66	0.90					
	Between 40-49	86	**2.44**	0.91					
	50 and 50^{+}	17	2.90	0.75					
	Total	430	2.67	0.91					
Virtual Communication	**Between 20-29**	85	**2.03**	0.92	3.728	**.011**	**Between 40-49**	**0.30**	**.046**
	Between 30-39	242	1.86	0.74					
	Between 40-49	86	**1.72**	0.71					
	50 and 50^{+}	17	**2.26**	0.82			**Between 40-49**	**0.54**	**.044**
	Total	430	1.88	0.79					
Emotional State	Between 20-29	85	2.49	1.02	1.196	.311			
	Between 30-39	242	2.48	0.93					
	Between 40-49	86	2.26	0.92					
	50 and 50^{+}	17	2.43	0.78					
	Total	430	2.43	0.94					

As can be seen in Table 11 when the p-values obtained as a result of the F-test (ANOVA) were examined, the social media addiction level of the academicians did not differ only in terms of "Emotional State" sub-factor by age. However, it was observed that there was a significant difference according to age in terms of "General Dependence", "Virtual Tolerance", "Virtual Interaction" and "Virtual Communication" sub-factors. A posthoc multiple comparison tests was conducted to determine between which age groups this difference occurred.

When the p-values obtained as a result of the multiple comparison test were examined, it was seen that the difference in social media addiction levels among academicians was especially between the 20-29 age group and the 40-49 age group. However, there was a significant difference between the 40-49 age group and the 50 and over age group.

One may see in Table 11 that, when the average values of the social media addiction levels of academicians were analyzed according to age, addiction levels were found to be the highest in the 20-29 age group in terms of Virtual Tolerance (Slacking) and Emotional State sub-factors and the total of the scale (general addiction) and it is also seen that addiction level was the most in the age group of 50 and more in terms of Virtual Interaction and Virtual Communication sub-factors. On the total scale, the addiction levels of academicians in the 40-49 age group were found to be the lowest on average. This situation can be explained by the fact that middle-aged academicians generally get prepared for the associate professorship and focus on their academic studies, especially at these ages.

When the p-values obtained as a result of the multiple comparison tests were examined, it was seen that the difference in social media addiction levels among academicians was especially between the 20-29 age group and the 40-49 age group. However, there was a significant difference between the 40-49 age group and the 50 and over age group.

Analyzing the Differences of Social Media Addiction among Academicians According to Academic Title: To determine whether social media addiction among academicians differed according to the academic title, the F-test (ANOVA) was conducted as more than two categories were belonging to the academic title.

Table 12. Mean Scores of Social Media Addiction Level Among Academicians by Academic Title

	(I) Academic Title	N	Mean	Std. Deviation	F	Sig.	(J) Academic Title	Mean Difference (I-J)	Sig.
General Addiction	**Research Assistant**	139	**2.49**	0.73	3.033	**.017**	**Professor**	**0.34**	.072
	Instructor	115	2.44	0.70					
	Ass. Prof.	122	2.27	0.64					
	Associate Professor	30	2.20	0.68					
	Professor	24	**2.15**	0.85					
	Total	430	2.38	0.71					
Virtual Tolerance (Slacking)	**Research Assistant**	139	**2.61**	0.91	3.691	**.006**	**Professor**	**0.44**	**.039**
	Instructor	115	2.59	0.91					
	Ass. Prof.	122	2.30	0.77					
	Associate Professor	30	2.26	0.80					
	Professor	24	**2.17**	0.97					
	Total	430	2.47	0.88					
Virtual Interaction	Research Assistant	139	2.79	0.92	1.375	.242			
	Instructor	115	2.69	0.89					
	Ass. Prof.	122	2.57	0.90					
	Associate Professor	30	2.51	0.76					
	Professor	24	2.50	1.10					
	Total	430	2.67	0.91					
Virtual Communication	Research Assistant	139	1.93	0.81	.658	.621			
	Instructor	115	1.93	0.78					
	Ass. Prof.	122	1.81	0.73					
	Associate Professor	30	1.75	0.80					
	Professor	24	1.88	0.99					
	Total	430	1.88	0.79					
Emotional State	**Research Assistant**	139	**2.58**	0.95	2.534	**.040**	**Professor**	**0.58**	**.040**
	Instructor	115	2.45	0.95					
	Ass. Prof.	122	2.38	0.93					
	Associate Professor	30	2.27	0.86					
	Professor	24	**2.00**	0.88					
	Total	430	2.43	0.94					

When the p-values obtained as a result of the F-test (ANOVA) were examined, it was seen that the social media addiction level of the academicians did not differ according to the academic title in terms of "Virtual Interaction" and "Virtual Communication" sub-scales; however, it was observed that there was a significant difference according to the academic title in terms of both "General Dependence", "Virtual Tolerance" and "Emotional State" sub-factors. A post-Hoc multiple comparison test was conducted to determine among which academic titles this difference was.

The result of the multiple comparison tests as seen in Table 12, showed that there was a significant difference between research assistants and assistant professors in terms of "Virtual Tolerance (Slacking)" sub-factors, and there was also a significant difference between research assistants and professors in terms of "Emotional State" sub-factor.

When the average values of the social media addiction levels of the academicians were examined by academic title, it was observed that as the academic title increased, social media addiction decreased in all sub-factors except "General Addiction" and "Virtual Communication" sub-factor as seen in Table 12.

DISCUSSION

As a result of today's conditions and technological developments, social media addiction is becoming more and more common in all segments of society. When the literature on social media addiction is examined, it is noteworthy that in our country, studies for young people are predominant. There are scarcely any studies on the relationship between social media and addiction for academicians. Based on this result, the present study aimed to reveal the social media addiction of academicians. And in the study, two main results were tried to be reached. The first was to reveal the validity and reliability of the scale used, and the second was to examine whether the social media addiction levels of academicians differed according to demographic characteristics, different from the study conducted by Şahin and Yağcı (18). For this purpose, 18 items of the 20-item SMAS-AF Scale developed by Şahin and Yağcı, a five-point Likert type (excluding the 2 items coded in reverse), were used and the scale was applied to 430 academicians. The result of the exploratory factor analysis showed that the scale had a 4-factor structure (Virtual Tolerance (Slacking), Virtual Interaction, Virtual Communication, and Emotional State sub-factors). The fit index values obtained as a result of the confirmatory factor analysis performed to verify this four-factor structure of the scale $\chi^2/df = 3.708 \leq 5$, $0.85 \leq GFI = 0.885$, $SRMR = 0.0629 \leq 0.08$, $RMSEA = 0.079 \leq 0.08$) showed that the scale had a good fit. For the total of the scale the internal consistency coefficient (Cronbach Alpha coefficient) was found as 0.895, 0.844 for Virtual Tolerance, 0.760 for Virtual Interactions, 0.721 for Virtual Communication, and 0.690 for Emotional State sub-factors. The analysis made revealed that the scale used to measure the social media addiction levels of academicians was valid and reliable.

As a result of the analyzes conducted to determine whether the social media addiction levels of the academicians differed according to gender, marital status, age, and academic title, although it was determined that the addiction level of female academicians was higher than that of males in terms of gender in total and sub-factors (except for the Virtual Communication sub-factor), this difference was not statistically significant.

In terms of marital status, a statistically significant difference emerged in the overall scale and the Virtual Tolerance (Loafing) sub-dimension, and when the average values were analyzed, it was seen that the social media addiction of single academicians was higher than the married ones. If this situation is interpreted as a result of the fact that married individuals have a family that should take time, it can be said that marital status is effective in social media addiction.

The current findings showed no significant difference in terms of "Emotional State" sub-factor according to age. However, a significant difference emerged especially between the 20-29 age group and the 40-49 age group in terms of the dimensions of "General Dependence", "Virtual Tolerance", "Virtual Interaction" and "Virtual Communication" sub-factors. Also, the social media addiction level of the academicians in the 40-49 age group was the least in all dimensions and the overall scale. This situation raises the possibility that academicians in the 40-49 age group, which can be described as middle age, are in the period of preparing for the associate professorship and focusing on academic studies in the most intensive.

Finally, the level of social media addiction among academics did not differ in terms of "Virtual Interaction" and "Virtual Communication" sub-factors according to the academic title; however, there was a significant difference in terms of both "General Dependence", "Virtual Tolerance (Slacking)" and "Emotional State" sub-factors. Also, there was a significant difference between research assistants and assistant professors in terms of "Virtual Tolerance (Slacking)" sub-factors; and there was a significant difference between research assistants and professor doctors in terms of the "Emotional State Factor" sub-factor. In the total of the scale (general addiction) and in all sub-dimensions except the Virtual Communication, social media addiction decreased as the academic title increased.

CONCLUSION

As a result, we concluded that the scale used was a measurement tool that could be used to determine the social media addiction levels of academicians, single academicians were more addicted than the married ones, young and old academicians were more addicted than the middle-aged ones, and social media addiction decreased as the academic title increased.

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RESEARCH ARTICLE

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Evaluation of the Effect of Comorbid Bronchiectasis on Quality of Life in Patients with Chronic Obstructive Pulmonary Disease

ABSTRACT

Objective: The objective of this study was to evaluate the effect of comorbid bronchiectasis on quality-of-life in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods: 103 patients were diagnosed with COPD were included in our study. Spirometric measurements were made. The following measurement tools were used to collect data: 6-Minute Walk Test (6MWT), Modified Medical Research Council (mMRC) dyspnea scale, COPD Assessment Test (CAT), St. George Respiratory Questionnaire (SGRQ), and Short Form 36 (SF-36) quality-of-life questionnaire. Furthermore, all the patients' high Resolution Computed Tomography (HRCT) images for the last three years were included in the study.

Results: 93.2% of the patients were male, with a mean age of 64.79 ± 9.35 years. It was found that SGRQ and SF-36 quality of life scores decreased to approximately half of the full score in all patients. The volume/forced vital capacity (FEV1/FVC) values in the first second of forced expiration were significantly lower in the group with bronchiectasis. A significant correlation was found to exist between the patients' mMRC dyspnea scale and CAT scores, 6MWT distances, and all subscales of SGRQ and SF-36. In addition, a significant correlation was also found to exist between FEV1 values and all subscales of SGRQ, and between subscales of SF-36.

Conclusions: In our study, when we compared the quality-of-life scores of the patients with COPD and bronchiectasis with those with COPD alone, we found that the quality-of-life of both groups was impaired, but there was no significant difference between them.

Keywords: Bronchiectasis, Chronic Obstructive Pulmonary Disease, Quality of Life.

Kronik Obstrüktif Akciğer Hastalığı Olan Hastalarda Komorbid Bronşektazinin Yaşam Kalitesine Etkisinin Değerlendirilmesi

ÖZET

Amaç: Bu çalışmanın amacı Kronik Obstrüktif Akciğer Hastalığı (KOAH) olan hastalarda eşlik eden bronşektazinin yaşam kalitesine etkisini değerlendirmektir.

Gereç ve Yöntem: Çalışmamıza KOAH tanısı konan 103 hasta dahil edildi. Spirometrik ölçümler yapıldı. Veri toplamak için, 6 Dakika Yürüme Testi (6MWT), Modifiye Tıbbi Araştırma Konseyi (mMRC) dispne ölçeği, KOAH Değerlendirme Testi (CAT), St. George Solunum Anketi (SGRQ) ve Kısa Form 36 (SF-36) yaşam kalitesi anketini içeren ölçüm araçları kullanıldı. Ayrıca tüm hastaların son üç yıla ait yüksek Çözünürlüklü Bilgisayarlı Tomografi (HRCT) görüntüleri çalışmaya dahil edildi.

Bulgular: Hastaların %93,2'si erkek olup, yaş ortalaması 64,79 ± 9,35 yıldı. Tüm hastalarda SGRQ ve SF-36 yaşam kalitesi puanlarının tam puanın yaklaşık yarısına kadar azaldığı bulundu. Zorlu ekspirasyonun ilk saniyesindeki volüm/zorlu vital kapasite (FEV1/FVC) değerleri bronşektazi tanılı grupta anlamlı olarak daha düşüktü. Hastaların mMRC dispne skalası ile CAT skorları, 6DYT mesafeleri ve SGRQ ve SF-36'nın tüm alt ölçekleri arasında anlamlı bir ilişki bulundu. Ayrıca FEV1 değerleri ile SGRQ'nun tüm alt ölçekleri ve SF-36'nın alt ölçekleri arasında da anlamlı bir ilişki bulundu.

Sonuç: Çalışmamızda KOAH tanılı ve bronşektazi tanılı hastaların yaşam kalitesi puanlarını tek başına KOAH tanılı hastalarla karşılaştırdığımızda her iki grubun yaşam kalitesinin bozulduğunu ancak aralarında anlamlı bir fark olmadığını bulduk.

Anahtar Kelimeler: Bronşektazi, Kronik Obstrüktif Akciğer Hastalığı, Yaşam Kalitesi

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar inflammation, generally resulting from significant exposure to noxious gases and particles (1). On the other hand, bronchiectasis is a condition that causes permanent dilatation of the bronchi and destroys the elastic and muscular components of their walls, usually due to acute or chronic infection (2,3). It has been reported that patients with bronchiectasis have more frequent hospitalizations, more severe airflow limitation, higher pulmonary artery pressure, and more extended stay in intensive care unit and hospital than those without bronchiectasis. However, despite all these negative effects, it has also been reported that bronchiectasis does not increase mortality (2,3).

COPD and bronchiectasis have many common features both physiopathologically and clinically. Both diseases are common particularly in the elderly; therefore, it is possible to see patients with simultaneous COPD and bronchiectasis. It has been reported that 50% of patients with moderate and advanced COPD have bronchiectasis and there is a relationship between the two, suggesting that COPD may be a risk factor for bronchiectasis (4,5)

Previous research conducted with COPD patients shows that High-Resolution Computed Tomography (HRCT) studies provide direct measurements of pulmonary pathologies, and there is a high correlation between some clinical measurements commonly used in COPD patients (volume in the first second of forced expiration (FEV1), C-reactive protein (CRP), sedimentation rate, exacerbation) (6). Pulmonary function measurements are used to measure how much the respiratory system is affected by COPD. In addition to pulmonary function measurements, it is also recommended to use ancillary assessments such as quality-of-life and field tests to determine the patient's quality-of-life and activity level. The social and physical needs of individuals with COPD can be better determined by a realistic assessment of their quality-of-life and participation in activities (7).

This study makes a comparison between patients with COPD and bronchiectasis and those with COPD alone in terms of quality-of-life.

MATERIAL AND METHODS

Patients who were diagnosed with COPD in the Chest Diseases Polyclinic of the local University Training and Research Hospital by a chest diseases specialist (pulmonologist) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria between January 2019 and April 2019 were included in this cross-sectional study.

Patients who were 40 years and older and diagnosed with COPD according to the GOLD (2019) criteria (postbronchodilator; volume in the first second of forced expiration/forced vital capacity (FEV1/FVC) <70%), had no exacerbation for at least four weeks, were in a stable period, had the cognitive ability to read, understand, and respond, had HRCT taken within the last three years, agreed to participate in the study, and gave their written consent were included in the study. On the other hand, patients who had physical and mental disabilities, could not perform the pulmonary function test (PFT), did not volunteer to participate in the study, and were unable to perform the 6-minute walk test (6 MWT) (respiratory failure, congestive heart failure, unstable angina, risk of myocardial infarction, neurological disorder/disease, patients with musculoskeletal problems, blood pressure of 90/50 mm/Hg and below or 180/100 mm/Hg and above) were excluded from the study.

A socio-demographic and clinical information form was prepared by the researchers to collect data on age, gender, education, occupation, monthly income, smoking status, presence of other disease and COPD exacerbation, the number of hospitalizations in the last year, and the number of emergency visits in the last year (staying in the emergency room for less than 24 hours).

Modified Medical Research Council (mMRC) dyspnea scale, COPD Assessment Test (CAT), St. George Respiratory Questionnaire (SGRQ), and Short Form 36 (SF-36) quality-of-life scale were administered through face-to-face interviews.

6 MWT was applied to all participants under the supervision of the researcher. The distance they walked at the end of the time was recorded in meters. Percentage of arterial O_2 saturation, arterial blood pressure (mmHg), heart rate (min), and dyspnea grade (Modified Borg Scale) were recorded using an oxygen probe before and after the test.

An experienced technician made the lung volume measurements using a Spirolab III color LCD device. Measurements were made as per the criteria defined by the American Thoracic Society/European Respiratory Society (ATS/ERS) in 2005 (8).

The Modified Medical Research Council (mMRC) dyspnea scale is a 5-digit scale consisting of progressively increasing degrees of dyspnea, from Stage 0 (I am breathless only during strenuous exercise) to Stage 4 (I am unable to leave the house due to shortness of breath or I am out of breath while dressing and undressing). The higher the scale score, the more severe the dyspnea perception (9).

The COPD Assessment Test (CAT) is an 8-item scale that evaluates health status in COPD (10). Its validity and reliability were tested in Turkey by Yorgancıoğlu et al. (11). Each question is scored between 0 and 5 (0 is the best and 5 is the worst).

St. George Respiratory Questionnaire (SGRQ) is used to assess the health-related quality-of-life in patients with COPD. It includes symptoms, activity, and impact on daily life. Scores vary between 0 and 100, and 0 represents the best health condition and 100 the worst health condition (12). The Turkish validity and reliability study of the SGRQ quality-of-life questionnaire was carried out by Polatlı et al. (13).

Short form-36 (SF-36) quality-of-life scale consists of 36 questions under the following 8 main sections: physical function, social function, physical role difficulty, mental state role, mental health, energy/vitality, pain, and general perception of health. Each main section is scored between 0 and 100. 0 indicates the worst health, and 100 the best health (14). The Turkish validity study of the scale was conducted by Koçyiğit et al. (15).

All the patients' HRCT scans taken using a 16-detector spiral CT scanner (Toshiba Alexion, Tokyo, Japan) within the last three years were used in the study. In addition, the same expert radiologist evaluated the images on a workstation (Vitreasoftware 6.5, VitalImages, Toshiba Medical Systems). The scoring system reported by Silvia et al. (16) was used for HRCT findings.

Statistical Analysis: The obtained data were analyzed using SPSS software package (v.21). Continuous variables were expressed in mean ± standard deviation (SD), and qualitative variables in numbers and percentages. The Chi-square test was used for comparing categorical variables between groups. Kolmogorov Smirnov test was used to test the normality of the continuous variables. Since the data were not normally distributed, Mann-Whitney U test was used to compare two groups, and Kruskall-Wallis H test to make a comparison between three or more groups. Finally, the relationship between the measured variables was evaluated using Spearman's ordinal number correlation. The statistical significance was set at 5%.

The study was carried out upon the approval of the Ethics Committee of Non-Invasive Clinical Researches, Faculty of Medicine, the local University (Date: January 11, 2019, Approval No: 1/11).

RESULTS

103 COPD cases followed-up in the Chest Diseases Polyclinic of the local University Training and Research Hospital were included in the study. Based on the HRCT data, the cases were grouped into two: those with bronchiectasis (59.2%, n=61) and those without bronchiectasis (40.8%, n=42).

The mean ages of the cases with and without bronchiectasis were 65.7 ± 9.3 years and 63.4 ± 9.5 years, respectively. As for the gender distribution of the groups, 95% (n=58) of the cases with bronchiectasis were male; 90.4% (n=38) of the cases without bronchiectasis were male. There was no significant difference between the two groups in terms of age and gender (p=0.266 and p=0.439, respectively), education level (p=0.689), exposure to harmful gases and particles (p=0.320), attack frequency (p=0.775), additional diseases (p=0.092) and smoking status (p=0.576) (Table 1).

Table 1. Sociodemographic and clinical characteristics of patients

Variables	All patients	With bronchiectasis	Without bronchiectasis	*p*
Age (year), (mean ± sd)	64.7 ± 9.4	65.7 ± 9.3	63.4 ± 9.5	0.266
Gender, *n* (%)				0.439
Female	7 (6.7)	3 (5)	4 (9.6)	
Male	96 (93.3)	58 (95)	38 (90.4)	
Education Status, *n* (%)				0.689
Literate and Primary school	73 (70.8)	44 (72.1)	29 (69)	
Middle school	16 (15.5)	8 (13.1)	8 (19)	
High school and University	14 (13.7)	9 (14.7)	5 (11.9)	
Exposed to harmful gases and particles in the occupation, *n* (%)				0.320
Yes	33 (32)	22 (36)	11 (26.1)	
No	62 (60.1)	36 (59)	26 (61.9)	
Did not worker	8 (7.9)	3 (4.9)	5 (11.9)	
Additional diseases, *n* (%)				0.092
Yes	42 (40.7)	29 (47.4)	13 (30.8)	
No	61 (59.3)	32 (52.6)	29 (69.2)	
Smoking status, *n* (%)				0.999
Smoking	40 (38.8)	21 (34.4)	19 (45.2)	
Never smoking	34 (33.0)	18 (29.5)	16 (38.1)	
Quit smoking	29 (28.2)	22 (36)	7 (16.6)	
Smokers, Package/year (mean ± sd) (min-max)	29.08±12.23 (10-60)	28.05±11.28 (10-50)	30.21 ± 13.43 (10-60)	0.576
Applying to the emergency department				0.818
Yes	48 (46.6)	29 (47.5)	19 (45.2)	
No	55 (53.4)	32 (52.4)	23 (54.7)	
Hospitalization				0.775
No	67 (65.0)	39 (64)	28 (66.6)	
1 time	18 (17.5)	10 (16.3)	8 (19)	
≥ 2 times	18 (17.5)	12 (19.6)	6 (14.2)	
Total, *n* (%)	103 (100)	61 (59.2)	42 (40.8)	

***n*, number; SD: standard deviation.**

FEV1/FVC (%) values were found to be significantly lower in the group with bronchiectasis than in the group without bronchiectasis (p=0.011) (Table 2).

Table 2. mMRC dyspnea scale scores, CAT scores, 6 MWT distances, and PFT parameters of the groups

	All patients mean±SD	With bronchiectasis mean±SD	Without bronchiectasis mean±SD	p
CAT	17.61 ± 10.27	17.44 ± 10.74	17.86 ± 9.67	0.831
mMRC dyspnea scale	2.56 ± 1.34	2.56 ± 1.38	2.57 ± 1.30	0.672
6 MWT (m) (min-max)	410.57 ± 154.14 (70-813)	409.46 ± 154.82 (110-650)	412.19 ± 155.01 (70-813)	0.801
FVC (lt)	2.55 ± 0.77	2.499 ± 0.75	2.62 ± 0.82	0.434
FVC (%)	68.53 ± 17.34	67.26 ± 18.13	70.38 ± 16.15	0.269
FVC (lt)	3.15 ± 17.20	4.25 ± 22.36	1.55 ± 0.55	0.209
FEV1 (%)	49.47 ± 15.73	47.43 ± 16.05	52.43 ± 14.96	0.101
FEV1/FVC (%)	56.47 ± 8.12	54.83 ± 7.85	58.857 ± 8.00	0.011

Mean: median value, SD: standard deviation, min: minimum, max: maximum, mMRC, Modified Medical Research Council; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; 6 MWT, 6-Minute Walk Test; PFT, pulmonary function test; FVC, forced vital capacity; FEV1, volume in the first second of forced expiration; FEV1/FVC, volume in the first second of forced expiration/forced vital capacity

It was found that there was a significant relationship between the number of admissions to the emergency department and the number of hospitalizations in the last year due to COPD acute exacerbations and all subscales of SF-36 quality-of-life scale and SGRQ. A significant negative correlation was found to exist between the FVC (lt) and FEV1 (lt) values of the patients and the number of admissions to the emergency department, and between the FVC (lt), FEV1 (lt), FEV1 (%), FEV1/FVC (%) values and the number of hospitalizations (Table 3).

Table 3. The relationship between admission to the emergency department and hospitalization, quality of life, and PFT values

	Admission to the emergency room		Hospitalization	
	r	**p**	**r**	**p**
SF-36 physical function	-0.536	<0.001	-0.633	<0.001
SF-36 physical restraint	-0.524	<0.001	-0.578	<0.001
SF-36 emotional restraint	-0.528	<0.001	-0.562	<0.001
SF-36 energy	-0.460	<0.001	-0.489	<0.001
SF-36 mental health	-0.301	0.002	-0.270	0.006
SF-36 social function	-0.424	<0.001	-0.511	<0.001
SF-36 pain	-0.358	<0.001	-0.426	<0.001
SF-36 general health	-0.416	<0.001	-0.319	0.001
SGRQ symptom	0.759	<0.001	0.633	<0.001
SGRQ activity	0.513	<0.001	0.618	<0.001
SGRQ effect	0.587	<0.001	0.596	<0.001
SGRQ total	0.631	<0.001	0.658	<0.001
FVC (lt)	-0.216	0.028	-0.381	<0.001
FVC (%)	-0.096	0.333	-0.136	0.171
FEV1 (lt)	-0.238	0.016	-0.404	<0.001
FEV1 (%)	-0.154	0.121	-0.215	0.029
FEV1/FVC (%)	-0.170	0.087	-0.258	0.009

SF-36, short form 36; SGRQ, St. George respiratory questionnaire; PFT, pulmonary function test; FVC, forced vital capacity; FEV1, volume in the first second of forced expiration; FEV1/FVC, volume in the first second of forced expiration/forced vital capacity

When the relationship between the number of cigarettes smoked and the quality-of-life was analyzed, it was found that there was a significant negative correlation between the number of cigarettes smoked and the following subscales of SF-36 quality-of-life scale: physical function (r=-0.374, p=0.019), energy (r=-0.360, p=0.024), and social function (r=-0.373, p=0.019). A significant and positive correlation was found to exist between all subscales of SGRQ (SGRQ; symptom r=0.388, p=0.013, activity r=0.568, p<0.001, affected r=0.409, p=0.009, total r=0.500, p =0.001).

When the mean scores for SF-36 quality-of-life scale and SGRQ were evaluated, it was found that the scores for the physical limitation (48.28 ± 48.01), emotional limitation (50.33 ± 48.69), and energy (51.67 ± 22, 34) scales were observed to decrease by approximately half of the full score. It was observed that the SGRQ symptom (48.01 ± 24.93) and activity (54.60 ± 29.39) scores

deteriorated more than the effect (32.67 ± 23.05) and total (41.99 ± 23.35) scores.

When the patients with and without bronchiectasis were compared in terms of quality-of-life parameters, no significant difference was found to exist between the groups (p>0.05). When the total score of HRCT findings (bronchiectasis, dilatation severity, peribronchial thickening, tree-in-bud, mucous plugs, air trapping, fibrotic collapse/consolidation, bulla, emphysema) of all cases, and SF-36 and SGRQ quality-of-life parameters were compared, no significant correlation was found to exist between the total score for HRCT findings and the quality-of-life scores (p>0.05).

When the relationship between HRCT data and PFT parameters was evaluated, it was found that the extent of bronchiectasis was negatively correlated with FEV1 (%) and FEV1/FVC (%), dilatation severity, and bullae, and FEV1/FVC (%) values were negatively correlated with emphysema. It was observed that there was a significant negative correlation between FEV1 (%) and FEV1/FVC (%) values (Table 4).

Table 4. The relationship between HRCT findings and PFT parameters

	FVC (%)		FEV 1 (%)		FEV 1/FVC (%)	
	r	**p**	**r**	**p**	**r**	**p**
Extension of bronchiectasis	-0.152	0.126	-0.208	0.035	-0.292	0.003
Dilation severity	-0.127	0.203	-0.169	0.088	-0.269	0.006
Peribronchial thickening	0.063	0.529	0.078	0.432	0.020	0.841
Tree in bud (budding tree view)	-0.087	0.382	-0.130	0.192	-0.174	0.078
Mucus plug	-0.099	0.319	-0.026	0.791	0.081	0.414
Air restraint	-0.126	0.204	-0.091	0.358	-0.006	0.952
Fibrotic collapse/consolidation	0.108	0.279	0.154	0.120	0.121	0.224
Bulla	-0.019	0.851	-0.097	0.331	-0.213	0.030
Emphysema	-0.080	0.420	-0.213	0.031	-0.299	0.002
Total HRCT	-0.098	0.325	-0.220	0.026	-0.368	<0.001

HRCT, high resolution computed tomography; PFT, pulmonary function test; FVC, forced vital capacity; FEV1, volume in the first second of forced expiration; FEV1/FVC, volume in the first second of forced expiration/forced vital capacity

When the relationship between the patients' mMRC dyspnea scale scores, CAT scores, SF-36 quality-of-life scores, and SGRQ scores were examined, it was found that there was a negative and significant relationship between mMRC dyspnea scale scores and the scores for all the subscales of SF-36 quality-of-life scale (p<0.001). A positive and significant relationship (p<0.001) was found to exist between the subscales. A negative and significant relationship (p<0.001) was found to exist between the CAT scores and the scores for all subscales of SF-36 quality-of-life scale, and a positive and significant relationship (p<0.001) between the CAT scores and the scores for all subscales of SGRQ (Table 5).

Table 5. Comparison of mMRC dyspnea scale and CAT scores of all cases in terms of quality of life

	mMRC		CAT	
	r	**p**	**r**	**p**
SF-36 physical function	-0.771	<0.001	-0.837	<0.001
SF-36 physical restraint	-0.634	<0.001	-0.685	<0.001
SF-36 emotional restraint	-0.611	<0.001	-0.692	<0.001
SF-36 energy	-0.548	<0.001	-0.640	<0.001
SF-36 mental health	-0.265	0.007	-0.423	<0.001
SF-36 social function	-0.511	<0.001	-0.570	<0.001
SF-36 pain	-0.513	<0.001	-0.570	<0.001
SF-36 general health	-0.408	<0.001	-0.390	<0.001
SGRQ symptom	0.703	<0.001	0.786	<0.001
SGRQ activity	0.743	<0.001	0.739	<0.001
SGRQ influence	0.700	<0.001	0.786	<0.001
SGRQ total	0.771	<0.001	0.831	<0.001

mMRC, Modified Medical Research Council; CAT, SF-36, short form 36; SGRQ, St. George respiratory questionnaire

When the relationships between all the cases' 6 MWT distances and FEV1 values and SF-36 quality-of-life scale and SGRQ scores were examined, it was observed that there was a

significant and positive relationship between their 6 MWT distances and scores for all subscales of SF-36 quality-of-life scale (p<0.001). It was observed that there was a significant and negative correlation between their 6 MWT distances and scores for all subscales of SGRQ (p<0.001). A negative and significant relationship was also found to exist between the patients' FEV1 (%) values and their scores for all subscales of SGRQ (p<0.05) and scores for the following subscales of SF-36 quality-of-life scale: physical function, physical limitation, emotional limitation, energy, social function, and general health. A positive and significant relationship (p<0.05) was found to exist between the subscales (Table 6).

Table 6. Comparison of 6 MWT distances and FEV 1 (%) values of all cases in terms of quality-of-life parameters

	6 MWT		**FEV1 (%)**	
	r	**p**	**r**	**p**
SF-36 physical function	0.719	<0.001	0.370	<0.001
SF-36 physical restraint	0.658	<0.001	0.269	0.006
SF-36 emotional restraint	0.674	0.001	0.274	0.005
SF-36 energy	0.508	<0.001	0.224	0.024
SF-36 mental health	0.343	<0.001	0.064	0.523
SF-36 social function	0.576	<0.001	0.250	0.011
SF-36 pain	0.463	<0.001	0.179	0.073
SF-36 general health	0.332	0.001	0.236	0.017
SGRQ symptom	-0.617	<0.001	-0.247	0.012
SGRQ activity	-0.662	<0.001	-0.356	<0.001
SGRQ influence	-0.637	<0.001	-0.320	0.001
SGRQ total	-0.693	<0.001	-0.348	<0.001

6 MWT, 6-Minute Walk Test; FEV1, volume in the first second of forced expiration; SF-36, short form 36; SGRQ, St. George respiratory questionnaire

DISCUSSION

In our study, the rate of bronchiectasis was found to be 59.2% among the patients followed-up with a diagnosis of COPD in our country. The parameters of quality-of-life were found to be low in all the cases with or without bronchiectasis.

The gold standard method in the diagnosis of bronchiectasis is Thorax HRC (17). Patel et al. (18) found bronchiectasis on HRCT in 27 (50%) of 54 COPD patients. O'Brien et al. (19) also reported bronchiectasis in 29% of 110 COPD cases screened by computed tomography of the thorax. Kurtulgan et al. (20) found bronchiectasis in 58.3%, bronchial wall thickening in 43.3%, and emphysema in 58.3% of 60 patients with COPD. In our study, bronchiectasis was detected in 61 (59.2%) of 103 COPD patients according to the HRCT images.

COPD is often accompanied by comorbidities that may have a significant impact on prognosis, and cardiovascular diseases are the most important of these comorbid diseases (21). It was reported that 54.3% of the patients had at least one other disease accompanying COPD, and the most common comorbidity was cardiovascular diseases with 30.4% (22). In our study, it was seen that 40.6% of the patients had a concomitant disease, and cardiovascular diseases ranked the first with 35.8%. It was found that the groups with and without bronchiectasis showed similar characteristics in terms of comorbidity distribution. This can be explained by the fact that smoking is an important risk factor for both diseases.

Donaldson et al. (23) conducted a study with 109 patients and reported that acute exacerbations in COPD negatively affected the decrease in FEV1. Gudmundson et al. (24) included 416 patients with COPD in their study to analyze the risk of readmission in patients with COPD and related risk factors and found that patients with low quality-of-life were admitted to the hospital more frequently. In our study, in accordance with the literature, the quality-of-life was found to be low within one year in the patients who were admitted to the emergency department or hospitalized more frequently due to COPD exacerbations

Cough, sputum complaints, and annual loss in FEV1 are thought to decrease with smoking cessation, and this positively affects the quality-of-life (25). In their study involving 102 cases followed-up with the diagnosis of COPD, Akbay et al. (26) found a correlation between the SGRQ symptom score and the duration of smoking (pack/year). Ince et al. (27) reported that there was no significant relationship between smoking, which is an important risk factor in the development of COPD, and quality-of-life scores. In our study, it was found that the quality-of-life of the patients was affected as the number of cigarettes smoked increased. According to both quality-of-life

questionnaires, as the number of cigarettes smoked increased, the limitation of physical activities of the patients increased. In addition, according to the SF-36 quality-of-life questionnaire, the patients' energy and social activities were affected by the number of cigarettes smoked.

In their study comparing COPD patients with a healthy control group, Ince et al. (27) reported that the scores for the limitations in physical function, vitality, and general health subscales of SF-36 quality-of-life scale were significantly higher in the COPD group than in the control group. In our study, consistent with the literature, it was observed that the quality-of-life deteriorated in patients with COPD, and the scores were low in the physical activity subscales in both quality-of-life questionnaires. In the SGRQ, both the activity score and the symptom score decreased by half in COPD patients, and according to the SF-36 questionnaire, physical limitation, emotional limitation, and energy scores were affected more than other sections. Since SF-36 evaluates general health in one of its subscales and SGRQ evaluates the effects of disease-specific symptoms, we believe that using both questionnaires together provide complementary information about the quality-of-life in COPD patients. When we analyzed the groups with and without bronchiectasis separately, it was found that the quality-of-life scores decreased in the group with bronchiectasis, but there was no significant difference between the two groups. We are of the opinion that in our cases bronchiectasis was not advanced due to the low rate of bronchiectasis spreading to the lobes in the lung, and therefore the symptoms did not reach a level that would further reduce the quality-of-life.

The diffuse airflow limitation is the most prominent functional finding in COPD. This restriction is demonstrated by forced expiration tests. FEV1 and FEV1/FVC ratios calculated from the forced expiration curve are the most reliable of these tests (20). In their study on 107 bronchiectasis patients, Sevgili et al. (28) reported that an obstructive-type respiratory dysfunction was observed in 72.9% of the patients in the pulmonary function test. Kurtulgan et al. (20) reported that the number of cases with bronchiectasis, emphysema, and air trapping was significantly higher in COPD patients with an FVC lower than 70%. As for the correlation between HRCT findings and PFT values in our study, it was observed that as the prevalence of bronchiectasis and emphysema areas increased, the FEV1 and FEV1/FVC values were negatively affected. The FEV1 and FEV1/FVC values were found to be low in our study, indicating obstruction in the airways, and this result was consistent with the literature.

The most prominent symptom in COPD patients is a chronic, progressive, and persistent dyspnea. Dyspnea increases especially during exercise and acute attacks and limits the patient's activities in daily life (29). One of the most important scales used in the evaluation of dyspnea is mMRC dyspnea scale. In their study comparing all scales of the SF-36 quality-of-life questionnaire with non-functional parameters, Soyyiğit et al. (30) reported that there was a significant relationship between mMRC dyspnea scale scores and the scores for the general health, physical function, social function, and energy scales. In our study, it was observed that mMRC dyspnea scale score was significantly correlated with all sub-parameters of both quality-of-life scales, and patients with high mMRC dyspnea scale scores had a low quality-of-life score, but there was no significant difference between the groups with and without bronchiectasis in terms of mMRC dyspnea scale score.

Although mMRC dyspnea scale only focuses on the shortness of breath, CAT provides a more comprehensive insight into the impact of COPD on patients' quality-of-life (11). In their study on 366 COPD patients, Miyazaki et al. (31) reported that the CAT scores correlated moderately well with all components of the SGRQ and SF-36 quality-of-life scale. In a multicenter study on 312 COPD patients aged 40-75 in Turkey, the relationship between CAT questionnaire and the SF-36 and SGRQ questionnaires was examined, and it was reported that there was a statistically significant relationship between the SF-36 scores and the CAT scores (13). In our study, it was observed that the patients' scores for all subscales of SGRQ and SF-36 worsened as their CAT scores increased, which was in line with the literature. However, no significant difference was found to exist between the groups with and without bronchiectasis in terms of CAT score.

Cömert et al. (32) reported that there was a significant relationship between SGRQ symptom score and activity score and FEV1 values measured after bronchodilator use. In our study, no significant difference was found to exist between the groups with and without bronchiectasis in terms of FEV1 value. When all the patients were evaluated, it was found that as FEV1 (%) decreased, the scores for all subscales of SGRQ deteriorated. On the other hand, in the SF-36 quality-of-life questionnaire, all subscales except mental health and pain were affected by the decrease in FEV1. In our study, it was found that the decrease in FEV1 value affected the quality-of-life negatively, which was consistent with the literature.

It is known that there is a relationship between the severity of COPD and walking distance. Lee et al. (33) reported a significant relationship between the 6 MWT distance and the

physical component of SF-36 quality-of-life scale and all components of SGRQ. In our study, it was observed that the quality-of-life was proportionally higher in the patients with a longer 6-MWT distance, and the 6-MWT distance was similar in the groups with and without bronchiectasis.

CONCLUSION

In our study, when the quality-of-life scores of the patients with COPD and bronchiectasis were compared with those with COPD alone, it was found that the quality-of-life of both groups deteriorated, but there was no significant difference between them. We believe that future studies can contribute to the literature by evaluating these two diseases together, examining the effect of this coexistence on symptoms, and showing how much the quality-of-life is affected by this coexistence.

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RESEARCH ARTICLE

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Evaluation of North Syrian Women Knowledge, Opinions and Attitudes Regarding Milk Banks and Milk Donation

ABSTRACT

Objective: To investigate Syrian mothers' knowledge, attitudes, and opinions on milk banks and raise awareness of the opening of milk banks in the region.

Methods: Our study was conducted hospitals in North Syria between 02/12/2020 and 02/03/2021. 536 women included in our study. Our questionnaire, which was written in Arabic to assess knowledge, opinions and attitudes toward milk donation and milk banks, was administered to participants during face-to-face interviews.

Results: All participants were female and Muslim, with a mean age of 29.79∓7.69 years. 47.2% of the participants agreed that a milk bank should be established, while 37.5% of the participants were against it. 81.3% women favored establishing a milk bank said that they would use the milk bank if they could not breastfeed (p=0.000). 49.4% were against establishing milk banks due to religious inconvenience. 41.5% of participants who favored establishing a milk bank and 14.4% of those who were against it indicated that the facility would have a positive impact on them under the guarantee of Turkey (p=0.000).

Conclusions: Due to religious views in Muslim societies, there is a negative attitude toward milk banks. Therefore, establishing robust registration systems, involving religious leaders in the process, providing accurate information, and educating the society will raise awareness and change the negative view.

Keywords: Milk Bank, Milk Donation, Syria, Wet Nursing.

Kuzey Suriyeli Kadınların Süt Bankaları ve Süt Bağışına İlişkin Bilgi, Görüş ve Tutumlarının Değerlendirilmesi

ÖZET

Amaç: Araştırmamızda Suriyeli annelerin süt bankası hakkındaki bilgi, tutum ve görüşlerini değerlendirmeyi ve bölgede süt bankalarının açılması için farkındalık oluşturmayı amaçladık.

Gereç ve Yöntem: Çalışmamıza Kuzey Suriye bölgesindeki hastanelere 02/12/2020-02/03/2021tarihleri arasında başvuran 536 anne dahil edilmiştir. Süt bağışı ve süt damlası merkezi'ne ilişkin bilgi, görüş ve tutumları değerlendirmeye yönelik Arapça olarak hazırlanan anketimiz katılımcılara yüz yüze görüşme tekniğiyle uygulanmıştır.

Bulgular: Katılımcıların tamamı kadın ve Müslüman, yaş ortalaması 29.79∓7.69 yıl idi. 47.2% katılımcı süt bankası kurulmalı, 37.5% katılımcı kurulmamalı görüşündeydi. Süt damlası merkezi kurulmasını onaylayanların 81.3%'ü bebeğini emziremediği durumda süt damlası merkezinden yararlanmak istediğini belirtti (p=0.000). Süt bankası kurulmamalı diyenlerin %49.4'ü dini sakıncalar nedeniyle istemediğini belirtti. Süt damlası merkezi kurulmasını destekleyen katılımcıların 41.5%'i, karşı çıkanların da 14.4% ü Türkiye güvencesi altında süt bankaları kurulmasının kendilerini olumlu etkileyeceğini ifade etti (p=0.000).

Sonuç: Müslüman toplumlarda dini çekinceler nedeniyle süt bankalarına olumsuz bir bakış mevcuttur. Bu nedenle sağlam kayıt sistemlerinin oluşturulması ve dini önderlerin de sürece katılması, yine toplumun doğru bilgilendirilmesi ve eğitilmesi farkındalık yaratacak ve olumsuz bakış açısını değiştirecektir.

Anahtar Kelimeler: Süt Bankası, Süt Bağışı, Suriye, Süt Annelik.

INTRODUCTION

Breast milk plays a critical and indispensable role in the nutrition of infants. The World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) recommend that infants be fed exclusively on breast milk for the first six months and continue to receive breast milk with complementary foods until at least two years of age (1). Despite this, breastfeeding rates are declining in many societies (2). The reason may be various problems caused by mother and baby. Prematurity and low birth weights are two important reasons.

Mothers whose babies are in the intensive care unit usually cannot provide enough breast milk to meet the needs of these babies. In such cases, donor breast milk is the best alternative (3). The risk of necrotizing enterocolitis (NEC) increases with the use of formula in high-risk infants, especially in preterm infants with very low birth weight (4). In cases where the mother's own breast milk cannot be used, the World Health Organization (2011) recommends the use of pasteurized donor breast milk from milk banks in preference to the use of infant formula (5).Studies have shown that the incidence of late-onset sepsis and food intolerances in infants fed on banked milk is low and the duration of discharge is shortened (1, 6).

In the Ottoman Empire, during the rule of Abdulhamid II., milk drop foundations and centers were established to provide breast milk to infants who could not receive it. Although wet nursery was practiced in Europe in the 19th century for infants who could not receive breast milk, it was not widely preferred due to the risk of infection. Breast milk banks were discovered as an alternative to wet nursery. The first breast milk bank was established in Vienna in 1909, followed by Boston (7). Milk banks spread throughout Europe in the 1930s and 1940s, but many of them closed with the advent of AIDS in the 1980s (8). In 1939, the number of milk banks in North America reached 12 and the standards for these facilities published by the American Academy of Pediatrics in 1943 were put into practice. In 1985, the North American Breastmilk Banks Association was founded (6). In turn, the European Milk Bank Association (EMBA) was founded in 2010. The European Milk Bank Association has280 affiliated milk banks with members from 29 countries (9). The largest breast milk bank system in the world is in Brazil; there are approximately 200 milk banks (10). The first milk bank in South Africa was established in 2000, and its number has since increased to 37 (11). Although the number of children who can benefit from milk banks is high in many developing and underdeveloped countries, the number of milk banks is very low (12). Breast milk banks are a system that is not yet accepted, especially in Muslim societies. This is because, according to religious beliefs, if a baby is nursed by a wet nurse, then that baby is considered milk sibling with the wet nurse's own children, even though they are not related to blood. These children are forbidden to marry each other (13). However, the first human milk bank in Iran was established in July 2016 at Al-Zahra Teaching Hospital in Tabriz (14).

Babies with premature births, anomalies, or low birth weight are often cared for in the intensive care units of Afrin, Azez Vatan, Jarablus, and Telabyad hospitals affiliated with Turkey's Ministry of Health in the Euphrates Shield area of operation. These infants have difficulty getting breast milk, so total parenteral nutrition therapy is provided. This treatment also comes at a high cost and cannot replace breast milk for a preterm infant. In this study, we aimed to determine the knowledge, attitudes, and opinions of Syrian women about milk banks and raise awareness about opening milk banks in the region.

MATERIAL AND METHODS

Study Design: Our study included randomly selected women over 18 years old who presented to Afrin, Azez Vatan, Jarablus, and Telabyad hospitals between 02/12/2020 and 02/03/2021and volunteered to participate in the study. Participants were initially informed about the study and their written and verbal consent were obtained according to the principles of the Helsinki Declaration Questionnaires were applied face-to-face to women who applied to the obstetrics outpatient clinics of these hospitals or whose babies were admitted to the neonatal intensive care units.

Study Setting and Selection Participants: In determining the population, women (34545 people) who applied to the obstetrics clinics of the hospitals or whose babies were hospitalized in the neonatal intensive care unit between1/12/2019 and 1/12/2020 were taken as the basis. The sample size and population of the study were calculated using the sample determination formula (Power analysis) in certain groups. According to this formula, the sample size was determined as 380, taking the reliability of 95%. A survey was conducted with 750 people who agreed to participate and were randomly selected from these applicants. We excluded the questionnaires that did not contain data and did not meet the inclusion criteria, and the questionnaires of 536 subjects were included in the study. Patients who were over 18 years of age and volunteered to participate in the study were included. Exclusion criteria were age less than 18 years, known mental disabilities, communication problems, requesting a fee for the survey by the applicants, and undetermined identities.

Obtaining Data: In our study, the questionnaire "Milk Drop Center Questionnaire", which determined the knowledge, opinions and attitudes about milk donation and milk drop centers, was completed by trained interviewers in face-to-face interviews. The name "Milk Drop Center", one of the first steps of milk bank in Ottoman period, was used in our survey. Our survey consisted of 2 sections and 27 questions. Nine (9) questions in the socio-demographic characteristics survey questionnaire were questions used in the general literature. Participants were asked; age, religion and religious denomination, educational and occupational status, ages and number of children, breastfeeding and pregnancy situation. Eighteen (18) questions in the "Information Form on Information, Opinions, and Attitudes Regarding Milk Donation and Milk Drop Center" were in accordance with the literature review of milk banks. With these questions, the need and importance of breast milk, their views on breastfeeding, their perspectives on milk bank in case of establishment of a milk bank, and the benefit status in case of establishment of a milk bank were evaluated. The Arabic of the questionnaire was translated by sworn translators with notarization.

Ethical Approval: Ethics committee approval for our study was obtained from The Ethics Committee of Hatay Mustafa Kemal University for non-interventional research (resolution number: 17) in 06/05/2021.

Statistical Analysis: Statistical analysis of the study were performed using Statistical Package for Social Sciences version 25.0 software for Windows (IBM SPSS Statistics for Windows version 21.0. Armonk, NY: IBM Corp., USA). Normality assumption was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. Explanatory statistics of variables are reported as mean±standard deviation, median (min-max), and n(%). For univariate analysis, Kruskal-Wallis, chi-square test, and Fisher-Freeman-Halton test were used, depending on the type of variable and availability of assumptions. In all statistical analysis, cases with a P value less than 0.05 were interpreted as statistically significant.

RESULTS

A total of 536 individuals participated in the study. All participants were female and the mean age was 29.79∓7.69 years. While all individuals were Muslims, the majority of them belonged to the Hanafi (67.7%, n=363) and Shafi (29.7%, n=159) sects. The educational and occupational status of the participants is shown in Table 1. The mean number of children the participants had was 3 (0-12). Among all participants, 482 (89.9%) of them reported that they were breastfeeding their child.

Table 1. Educational status and occupational distribution of the participants

Education	**n (%)**
Illiterate	81 (15.1%)
Literate	122 (22.8%)
Primary School	188 (35.1%)
Secondary School or higher	145 (27.1%)
Occupation	
Homemaker	339 (63.2%)
Nurse	40 (7.5%)
Teacher	37 (6.9%)
Cleaning staff	25 (4.7%)
Police	13 (2.4%)
Worker	13 (2.4%)
Computing	10 (1.9%)
Other	59 (11%)

When analyzing the responses to the Information Form on Information, Opinions and Attitudes Regarding Milk Donation and Milk Drop Center, 529 (98.7%) participants agreed that breast milk is important. Eighty-three (15.5%) participants indicated that they themselves had been wet nurses before, and 138 (25.7%) participants indicated that their children had ever been wet nursed before. Of the participants whose children were wet nursed, 25 (4.7%) were nursed by their sister, 21 (3.9%) by their co- sister-in-law, 21 (3.9%) by their neighbor, and 18 (3.4%) by their sister-in-law. 64.9% (n=348) of the participants reported that they would not want their baby to be breastfed by another mother even if they could not breastfeed their baby. The babies of 150 (28%) participants were treated in the ICU after delivery. When asked their opinion on the establishment of a milk drop center, 253 (47.2%) participants said it should be established, 174 (32.5%) said it should not be established and 109 (20.3%) participants were undecided. The answers given by the people to the questions about wet nursery and bank milk were as shown in Table 2.

Table 2. Participants' responses to the questions on the use of banked milk and wet-nursery

	Yes n (%)	**No n (%)**	**Undecided n (%)**
Is it all right to use the milk drop center when the mother's milk is insufficient?	191(35.6%)	277(51.7%)	68(12.7%)
In cases where breast milk is insufficient, is it appropriate to buy breast milk from trusted people?	182(34.0%)	291(54.3%)	63(11.8%)
Would you donate your milk to the milk drop center?	189(35.3%)	256(47.8%)	91(17.0%)
If a baby in the ICU needed breast milk, would you voluntarily donate your milk to them?	449(83.8%)	53(9.9%)	34(6.3%)
Do you think another mother's milk would be sufficient to feed your baby?	136(25.4%)	281(52.4%)	119(22.2%)
Would you use the milk drop center if you could not breastfeed your baby?	160(29.9%)	308(57.5%)	68(12.7%)

Most participants (59.6%, n=309) answered "negative" to the question "How does feeding your baby with another mother's milk affect the emotional bond between you and your baby?".

When asked what information should be obtained about the people who donate breast milk to the milk drop center, 335 (62.5%) of the participants answered "information about chronic diseases" and 262 (48.9%) participants answered "religion" (Figure 1). 76.7% (n=133) of the participants who did not want a milk bank to be established, stated that they did not want it because of the risk of disease transmission and 49.4% (n=86) because of religious objections. When asked about their opinion on the benefits of a center under the guarantee of Turkey, 166 (31%) people said that their opinion would not be influenced at all, 155 (28.9%) people said that it would be influenced positively, and 120 (22.4%) people said that it would be influenced negatively.

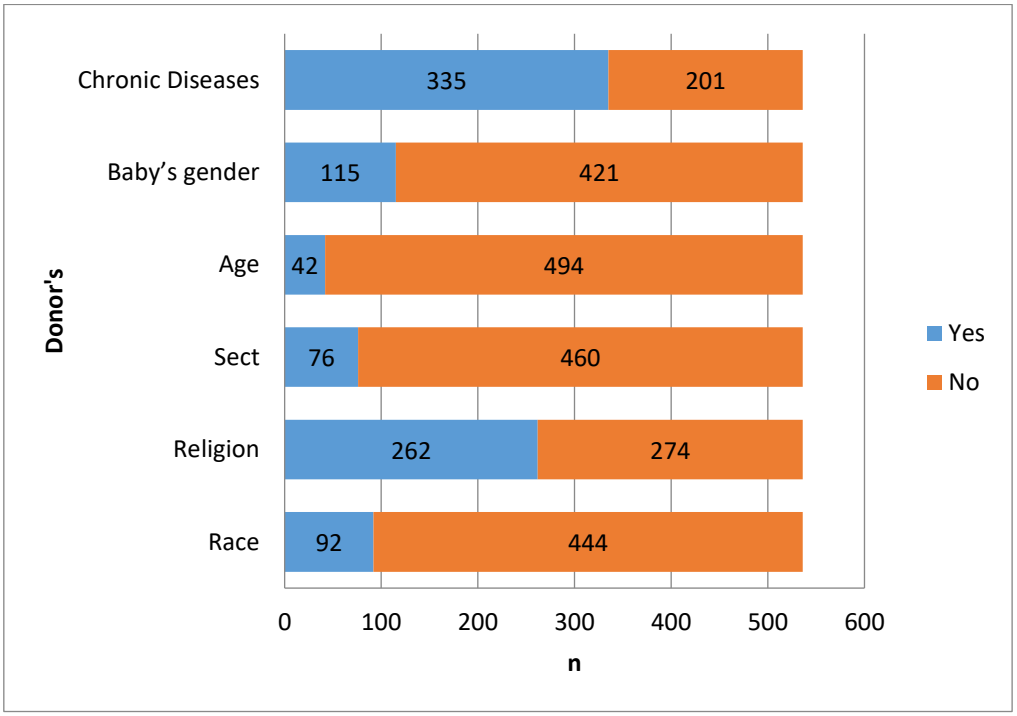

Figure 1. The characteristics required to know about the people who will donate breast milk to the milk drop center

The impact of the factors discussed in the study on the views on the establishment of the milk drop point is shown in Table 3. The mean age of those who were favored the establishment of milk drop point was higher than those who were against it or undecided about it (p=0.002). The number of children of the women who were favored establishing a milk drop point was also significantly higher (p=0.000). Most of those who were negative (90.2%) and undecided (88.1%) about the establishment of a milk drop point did not previously wet nurse (p=0.004). It was found that 86.2% of the participants who had a negative opinion about the establishment of a milk drop center had not previously had their children wet nursed (p=0.000). The participants who had a positive opinion about the establishment of a milk drop center were also significantly more likely to donate their milk if the center was established (p=0.000). Again, 81.3% of those who agreed with the establishment of a milk drop center indicated that they would be happy to use the milk drop center if they were unable to breastfeed their baby (p=0.000). A significant association was found between the idea of establishing a milk drop center and those who indicated that they would benefit from this center if it was established under the guarantee of Turkey (p=0.000). In our study, 41.5% of the participants who supported the establishment of a milk drop center indicated that it would affect them somehow if the center was established under the guarantee of Turkey. Of these individuals, 14.4% indicated that it would have a positive impact on them and 34.5% indicated that it would have a negative impact on them. 43.1% of those who support a milk drop center stated that they believed that another mother's milk would be enough to feed their baby, while 73.6% of those who did not support the milk bank stated that another mother's milk would not be enough to feed their baby (p=0.000). Most of those who did not support the establishment of a milk drop center (76.4%) felt that feeding their baby on another mother's milk would negatively affect the emotional bond between the mother and the baby. Among those who supported the establishment of a milk drop center, this percentage decreased to 14.9% (p=0.000).

Table 3. Comparison of sociodemographic characteristics, breastfeeding, wet-nursing and views on milk donation with opinions on establishing a milk bank

	What is your opinion on the establishment of a milk drop center?			
	Positive	**Negative**	**Undecided**	
	253(47.2%)	174(32.5%)	109(20.3%)	
				p
Age	30(17-47)	27(16-49)	29(15-48)	**0.002**
Number of children	4(0-12)	3(0-9)	3(0-11)	**0.000**
Sect				
Hanafi	166(65.6%)	117(67.2%)	80(73.4%)	0.436
Shafi	81(32.0%)	51(29.3%)	27(24.8%)	
Maliki	5(2.0%)	6(3.4%)	1(0.9%)	
Hanbali	1(0.4%)	0(0.0%)	1(0.9%)	
Education				
Illiterate	46(18.2%)	20(11.5%)	15(13.8%)	0.132
Literate	55(21.7%)	40(23.0%)	27(24.8%)	
Primary School	93(36.8%)	54(31.0%)	41(37.6%)	
Secondary School or higher	59(23.3%)	60(34.5%)	26(23.9%)	
Work status				
Working	167(66.0%)	110(63.2%)	80(73.4%)	0.197
Not Working	86(34.0%)	64(36.8%)	29(26.6%)	
Did you breastfeed your child / children?				
Yes	226(89.3%)	154(88.5%)	102(93.6%)	0.357
No	27(10.7%)	20(11.5%)	7(6.4%)	
Did you previously wet nurse?				
Yes	53(20.9%)	17(9.8%)	13(11.9%)	**0.004**
No	200(79.1%)	157(90.2%)	96(88.1%)	
Have your children been wet nursed before?				
Yes	92(36.4%)	24(13.8%)	22(20.2%)	**0.000**
No	161(63.6%)	150(86.2%)	87(79.8%)	
Has your baby been hospitalized in intensive care after birth?				
Yes	82(32.4%)	43(24.7%)	25(22.9%)	0.092
No	171(67.6%)	131(75.3%)	84(77.1%)	
Would you donate your milk to the milk drop center?				
I would	112(44.3%)	45(25.9%)	32(29.4%)	
I would not	91(36.0%)	116(66.7%)	49(45.0%)	**0.000**
Undecided	50(19.8%)	13(7.5%)	28(25.7%)	
Would you like to use the milk drop center if you are unable to breastfeed your baby?				
Yes	130(81.3%)	15(8.6%)	15(13.8%)	
No	97(38.3%)	150(86.2%)	61(56.0%)	**0.000**
Undecided	26(10.3%)	9(5.2%)	33(30.3%)	
Does the fact that the milk drop center is under the guarantee of Turkey influence your opinion on the use of the milk drop center?				
Yes, positively	105(41.5%)	25(14.4%)	25(22.9%)	**0.000**
Yes, negatively	39(15.4%)	60(34.5%)	21(19.3%)	
No	68(26.9%)	71(40.8%)	27(24.8%)	
Undecided	41(16.2%)	18(10.3%)	36(33.0%)	

DISCUSSION

Most of our participants indicated that they were against buying milk from a milk bank and donating milk to it. Similarly, in a study conducted in Turkey with health workers, it was found that most of them did not want to benefit from breast milk bank (1). In the study by Bhoola et al., most of the participants indicated that if it was culturally and religiously appropriate, they would be willing to become donors to a milk bank or purchase milk from it (11).Additionally, majority of our participants indicated that they could donate their milk to a baby in the intensive care unit. In the study by Ergin et al., most of the participants indicated that they could donate milk to a baby in need, but they would not donate their milk to the milk bank (15).Although it appears that religious reservations in Muslim populations influence attitudes toward milk banks, one can say that they

feel it is safer and religiously appropriate to donate if they know the baby and family for whom the milk is being donated.

In our study, similar to the literature, it was found that the major concern of participants who did not want a milk bank to be established was the risk of disease transmission. Similarly, in a study conducted in Kenya, it was found that most participants were concerned about the transmission of HIV and related diseases through breast milk. Also, in a study conducted in South Africa, it was found that most mothers were afraid of HIV transmission to their babies through donor milk (16, 17).

Most of our participants indicated that they would not prefer to use another person's milk or to benefit from milk delivery center, even if they could not breastfeed their own children. On the other hand, in a study conducted in Kenya, 59% of participants said they could use donor milk from a milk bank if they could not breastfeed their baby. Again, most of the participants who indicated that they could use donor milk were Christians (17).We believe that this difference is due to the different religious populations in the studies, with Muslim participants having a more negative opinion.

In a study conducted in Turkey, mothers indicated that they would not want to give their baby milk from a familiar person if their own milk was not sufficient (18). Similarly, most of the participants in our study indicated that it would not be appropriate to take breast milk from familiar people.

Wet nursing is a well-known and ancient method, especially in Muslim societies. Over time, the concept of wet infant feeding has also declined due to concerns such as infectious diseases. In our study, 15% of the participants used to be wet nurses. Again, it was found that 26% of the participants' children were wet nursed by one of their close relatives. In the study by Karadağ et al., most of the participants stated that it is possible to be breastfed by another person if the mother does not have milk (18). In another study conducted in Turkey, it was found that 8.7% of individuals wet breastfed and 7.2% of them had their babies wet breastfed by a relative (15). Considering that today's donor milk provided through milk banks has undergone serious screening and pasteurization processes, it is obvious that this milk is safer, but religious and cultural differences may prevent people from using milk banks.

Kimani et al. found that most participants did not think the race or ethnicity of the donors was important. Similarly, in our study, most participants stated that it was not necessary to ask about the donors' race or sect, and approximately half of them stated that it was not necessary to ask about their religion (17).

Even if the mothers did not openly state how they feel, there is a high possibility that they may feel helpless and inadequate if they cannot breastfeed their child and must use milk from another mother. These emotional conditionsmay lead the mothers to feel negative about using donor's milk. In parallel, most of our participants accept that breast milk plays an important role in infant health. However, most of them who did not support the establishment of a milk station stated that feeding their baby with another mother's milk would negatively affect the relationship between the baby and the mother. If mothers are more informed and educated about milk banks, their negative attitude toward the issue can be changed in positively and they can give their baby the proper attention and care without concerning about the misconceptions on the matter.

Similar to the literature, in this study, most mothers with babies in ICUs and more than half of the mothers whose babies were not in ICUs supported the establishment of milk banks. Pal et al founded that the preference rate for donor milk was significantly higher among mothers whose babies were cared for in the ICU than among mothers with healthy babies (19).

The proportion of our participants who were positive about the establishment of a milk drop center was significantly higher than the proportion of those who would donate their milk if the center was established; however, most of them indicated that they would be happy to use the milk drop center if they were unable to breastfeed their baby. We see that proper information and education of mothers and expectant mothers about milk banks can positively change people's views.

In places where there is no central authority, the positive effects of friendly and allied support in the process of rebuilding social trust are undeniable. In fact, in our study, 41.5% of the participants who supported the establishment of a milk drop center stated that its establishment would have a positive impact on them under the guarantee of Turkey, while 14.4% of those who opposed the establishment stated that this situation would have a positive impact on them.

CONCLUSION

Breast milk is an essential nutrient for infant feeding. Moreover, many studies in the literature have shown that the best alternative for infants who cannot receive breast milk for various reasons is donor breast milk. In Muslim societies such as Syria, there is a negative attitude toward milk banks due to religious reservations. In particular, the concept of having considered as milk siblings if breastfed by same mother and the religious prohibition of marriage for these people are seen as the leading obstacles. For this reason, it is important to establish reliable registration systems and

involve religious leaders in the process. Proper information and education of society will raise awareness and change the negative perception. With the financial and advisory support of international organizations, the establishment of milk banks in these regions can be advanced.

Limitations: Since our study was conducted on the Muslims, the results reflect only the perspective of this population. Another limitation of our study is that all of our participants were women; men could not be included in the study because sufficient number of participants could not be reached.

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RESEARCH ARTICLE

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Clinicopathological Features of Gastrointestinal Stromal Tumors and Review of the Literature: A Single Institution Experience

ABSTRACT

Objective: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasias of the gastrointestinal system (GIS). The malignancy potential of GISTs may vary ranging from indolent tumors to progressive malignant tumors. This study aims to define clinicopathological and immunohistochemical features of GISTs diagnosed in our institute with a review of the literature.

Methods: A total of 28 GIST cases were included in the study. The Hematoxylin&Eosin stained slides of surgical resection materials and cell blocks and immunohistochemistry performed slides were reviewed by a pathologist. The immunohistochemical expression with CD117, DOG-1, CD34, SMA, and S100 was scored between 0 and 3 points according to staining intensity. Descriptive statistics were used in the study. The demographic data, prognostic histopathological, and immunohistochemical findings are evaluated with the literature indications.

Results: Eleven of the cases were male and seventeen were female. The age range was 18-88. The most common site of GISTs was the stomach, followed by the small intestine, colorectal region, and, esophagus. Twenty of the tumors were resected surgically, four were endoscopic biopsy material and four were fine-needle aspiration biopsies. The tumor size in measurable materials ranged from 0,2 to 22 cm. The mitotic count in 50 HPF ranges from 0 to 10. Seven of the GISTs were high grade and the remaining 21 were low grade. The majority of the cases were composed of spindle cells, 3 were epithelioid and 3 were the mixed type with spindle and epitheloid cells.

Conclusions: A variety of criteria has been proposed to estimate the malignancy potential of GISTs and predict prognosis but definite prognostic criteria remain uncertain. Further studies with larger series of GISTs consisting of different types of biopsy materials may help define criteria to predict prognosis precisely.

Keywords: Gastrointestinal Stromal Tumors, CD117, DOG-1, CD34, Prognosis.

Gastrointestinal Stromal Tümörlerin Klinikopatolojik Özellikleri ve Literatürün Gözden Geçirilmesi: Tek Merkez Deneyimi

ÖZET

Amaç: Gastrointestinal stromal tümörler (GİST) gastrointestinal sistemin en sık görülen mezenşimal neoplazileridir. GİST'lerin malignite potansiyeli indolen tümörlerden progresif malign tümörlere kadar değişken olabilir. Bu çalışmada merkezimizde tanı almış GİST'lerin klinikopatolojik ve immünohistokimyasal özelliklerini literatür eşliğinde gözden geçirmek amaçlanmıştır.

Gereç ve Yöntem: Toplam 28 GİST olgusu çalışmaya dahil edilmiştir. Cerrahi rezeksiyon materyalleri ile hücre bloklarından hazırlanan Hematoksilen&Eozin boyalı preparatlar ile immünohistokimya uygulanmış preparatlar patoloji uzmanı tarafından değerlendirilmiştir. CD117, DOG-1, CD34, SMA ve S100 immünohistokimyasal ekspresyonları boyanma yoğunluğuna göre 0-3 puan arasında skorlanmıştır. Çalışmada deskriptif istatistikler kullanılmıştır. Demografik bulgular, prognostik histopatolojik ve immünohistokimyasal sonuçlar literatür eşliğinde değerlendirilmiştir.

Bulgular: Olguların 11'i erkek, 7'si kadındı. Yaş aralığı 18-88 arasındaydı. GİST'ler için en sık görülen lokasyon mide olup bunu ince barsak, kolorektal bölge ve özofagus takip etmekteydi. Tümörlerin 20'si cerrahi olarak çıkarılmış olup, 4'ü endoskopik biyopsi, kalan 4'ü ince iğne aspirasyon biyopsi materyaliydi. Tümör çapı ölçülebilen materyallerde tümör çapı 0,2 ile 22 cm arasındaydı. 50 büyük büyütme alanında mitoz sayısı 0 ile 10 arasındaydı. GİST'lerin 7'si yüksek dereceli, 21'i düşük dereceliydi. Olguların çoğunluğu iğsi hücrelerden oluşmakta olup, 3'ü epiteloid, 3'ü mikst tipteydi.

Sonuç: GİST'lerin malignite potansiyelini tahmin etmek için çeşitli kriterler öne sürülmüş olsa da kesin prognostik kriterler belirlenmemiştir. Çeşitli biyopsi materyallerinden oluşan daha büyük vaka serilerinde yapılacak çalışmalar prognozu daha kesin öngörebilecek kriterlerin belirlenmesine yardımcı olacaktır.

Anahtar Kelimeler: Gastrointestinal Stromal Tümör, CD117, DOG-1, CD34, Prognoz

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasias of the gastrointestinal system (GIS), derived by differentiation to the interstitial cells of Cajal (1). GISTs are rare tumors that indicate an incidence of 10-15 per million (2). They consist of less than 1% of all GIS tumors (3).

The majority of GISTs develop through activating mutations in KIT and/or platelet-derived growth factor receptor (PDGFR) (1). The oncogenic mutations in these genes result in activation of the tyrosine kinase receptor, which regulates proliferation and growth (4). The mutations in c-kit or platelet-derived growth factor receptor alpha (PDGFRA) exist in almost 85-90% of GIST cases (3). The remaining 10% cases are succinate dehydrogenase-deficient GISTs, NF1-associated GISTs, translocation-associated GISTs, and, BRAF V600E–mutated GISTs (3,5,6,7). Hirota et al. reported expression of CD117 (c-KIT) immunohistochemically is a key diagnostic marker for GISTs in the year 1998 (8). Positivity of CD117 helps in differential diagnosis to distinguish GISTs from other mesenchymal tumors such as leiomyomas and leiomyosarcomas (1). Immunohistochemically, almost up to 95% of GISTs are stained with CD117 (9,10). DOG-1 gene encodes a calcium-activated chloride and bicarbonate channel (11). DOG-1 is also an immunohistochemical marker that is frequently expressed in GISTs (up to 98%) and interstitial Cajal cells (12). Almost 70% of GISTs show positive staining with CD34 (13). GISTs may be stained with Smooth muscle actin (SMA), S100, and Desmin with less frequency (14). This study aims to define clinicopathological and immunohistochemical features of GISTs diagnosed in our institute with a review of the literature.

MATERIAL AND METHODS

The study was performed according to the tenets of the Helsinki Declaration and according to approval by the local Ethics Committee of the Duzce University Medical School (prot. No 2022/56 of April 2022).

A total of 29 GIST cases diagnosed in 2012–2022 were included in the study. The inclusion criteria were (i) histopathologic diagnosis of GIST; (ii) sufficient clinical history; and (iii) sufficient pathology material for immunohistochemical analysis. The exclusion criteria were (i) insufficient tumor tissue for immunohistochemistry and (ii) insufficient histological and immunohistochemical features for the diagnosis of GIST. All cases were recruited from the archives of the Pathology Department of Duzce University School of Medicine. Demographic data such as age, gender, tumor size, the type of biopsy material, and localization of tumor were obtained from pathology reports and patient files. Descriptive statistics (mean, standard deviation, number, and percentage) were used in the study.

The Hematoxylin&Eosin (H&E) stained slides of surgical resection materials and cell blocks and immunohistochemistry performed slides with CD117, DOG-1, CD34, SMA, S100, and ki67 were reviewed by a pathologist. The assay was performed using the Ventana Benchmark XT (Ventana-Roche Diagnostics, Meylan, France). The localization of the tumor, growth pattern, mucosal ulceration, necrosis, tumor grade, cell type (spindle, epithelioid or mixed), and surgical margins were evaluated from the H&E slides. Tumor grade, cell types, and pathological stage were defined due to criteria of the World Health Organisation (WHO) classification of tumors of the digestive system, 2019 (2). Cellularity and pleomorphism are determined as low, mild, or high. Categorization of tumors was made based on United States (US) Armed Forces Institute of Pathology (AFIP) data to define the relationship between mitotic rate and tumor size to the prognosis of GISTs. The immunohistochemical expression with CD117, DOG-1, CD34, SMA, and S100 was scored between 0 and 3 points according to staining intensity. No staining was considered 0, light staining 1, moderate staining 2, and strong staining 3 points. Staining percentage points were determined using a manual count of stained cells and the total number of tumor cells. The staining percentage has been evaluated in 5 categories: Negative, less than 25%, between 25%-50%, between 50%-75%, and more than 75%. The mitotic count from the fifty fields (/50 HPF) with the highest number of mitotic figures was determined. After the hotspot was identified under low magnification, the ki-67 labeling index was determined as a percentage by a manual count.

RESULTS

Eleven of the cases were male and seven were female. The age range was 18-88, with a mean age of 62.21. The median age was calculated as 65.5. The most common site of GISTs was the stomach (n=14), followed by the small intestine (n=10), colorectal region (n=3), and, esophagus (n=1). Twenty of the tumors were resected surgically, four were endoscopic biopsy material and four were fine needle aspiration (FNA) biopsies. The symptoms at presentation vary. Seven of the patients had abdominal masses. Five patients had abdominal pain and 3 had dyspepsia, 1 patient had fatigue, 1 patient had difficulty with swallowing and, 2 patients had reflux. Three patients applied to the hospital with gastrointestinal bleeding and 1 patient with ileus. Four cases were

detected incidentally during obesity surgery and 1 during hydatid cyst operation. The tumor size in measurable materials ranged from 0,2 to 22 cm and the mean tumor size was 5.27 cm. In tissue biopsy materials 17 of the tumors have expansive borders, and 7 show infiltrative borders. Except for the slides prepared from cell blocks of FNA materials, 6 of the cases have shown mucosal ulceration. Necrosis was present in 6 cases, 4 of them are high grade. The mitotic count (MC) in 50 HPF ranges from 0 to 10. Seven of the GISTs were high grade and the remaining 21 were low grade. The majority of the cases were composed of spindle cells (22), 3 were epithelioid and 3 were the mixed type with spindle and epitheloid cells. The cellularity of the GISTs was low in 11 cases, mild in 12, and high in 5. Two of the tumors with mild cellularity were high grade. Pleomorphism was low in 19 cases, mild in 7, and high in the remaining 2. Due to TNM classification, in tumor size measurable cases, 6 of GISTs were pT1, 7 were pT2, 7 were pT3 and 2 were pT4. For the tumors with measurable tumor size, 6 of the GISTs located in the stomach were category 1, 2 were category 2 and 1 was category 5. Only one case was category 1 in small bowel GISTs; 3 were category 2, 2 were category 3a, 3 were category 6a and 1 was category 6b. The colorectal localized GISTs were categories 3a,6a, and 6b. All GIST cases showed positive staining with CD117. The majority of the cases showed a staining percentage of more than 75% (n=23). The staining percentage between 50-75% was observed in remained 5 cases. In 15 cases CD117 staining was strong enough to take 3 points, 11 cases showed moderate staining and 2 cases had light staining with 1 point (Fig.1). DOG-1 immunoreactivity was seen in more than 75% of 18 patients, between 50-75% in 5, between 25-50% in 3, and less than 25% in one case. The intensity of staining points with DOG-1 were 3 in 12, 2 in 10, and 1 in 5 cases. CD34 was stained more than 75% in 17 cases, between 50-75% in 4 and less than 25% in one case. Six cases were negative with CD34. The satining intensity of CD34 was strong in 16 cases (3 points), moderate in 5 (2 points) and, light in 1 (1 point). Most cases were negative with SMA, but 3 cases showed focal positive staining (<25%). No immunoreactivity with s100 was observed in the majority of the cases, only in 2 cases showed focal positivity (<25%) with s100. The ki67 labeling index is between 1 to 50% in hot spots, but in the majority of the cases (24/28), the proliferation index was under 10% (Fig.2). Three cases had metastases. Two high-grade tumors had metastases to the liver and lymph nodes, and one low-grade tumor had a metastatic tumor in the liver.

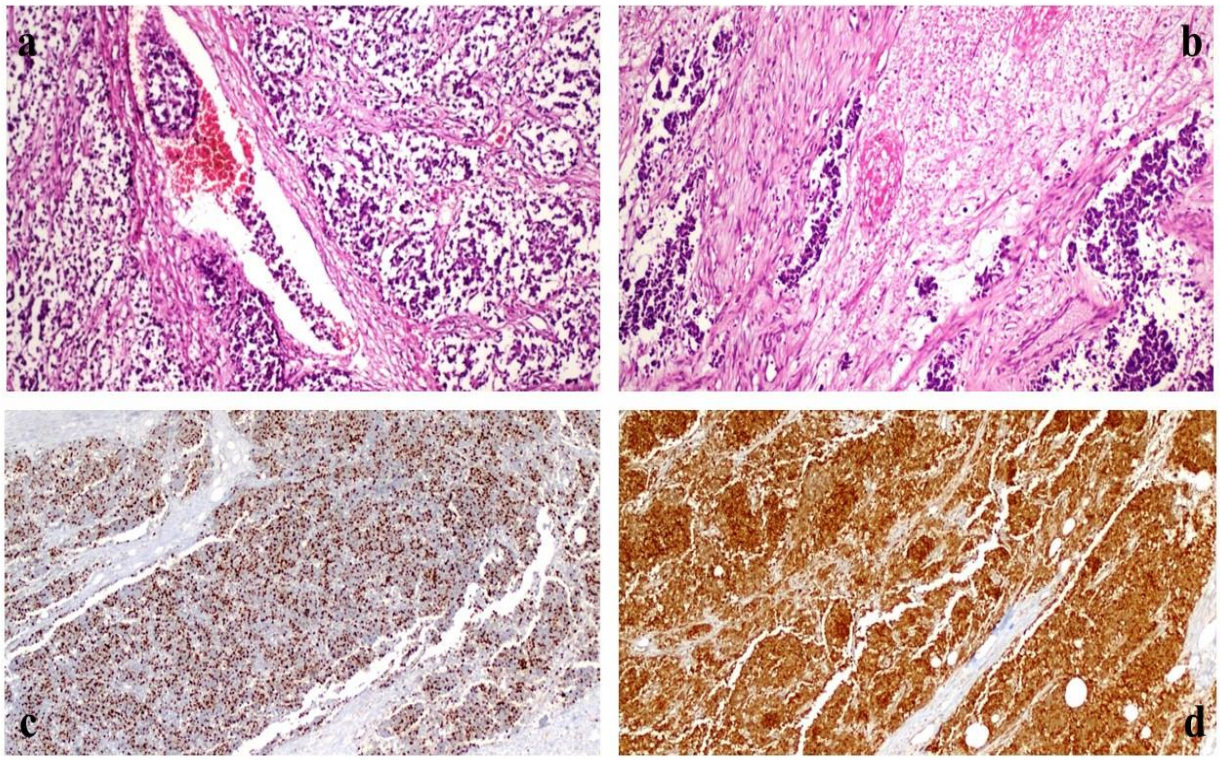

Figure 1. The tumor composed of small epithelioid morphology showed vascular and perineural invasion (H&E, x10, a and b), with a high ki67 labeling index (c) and diffuse CD117 immunoreactivity (d).

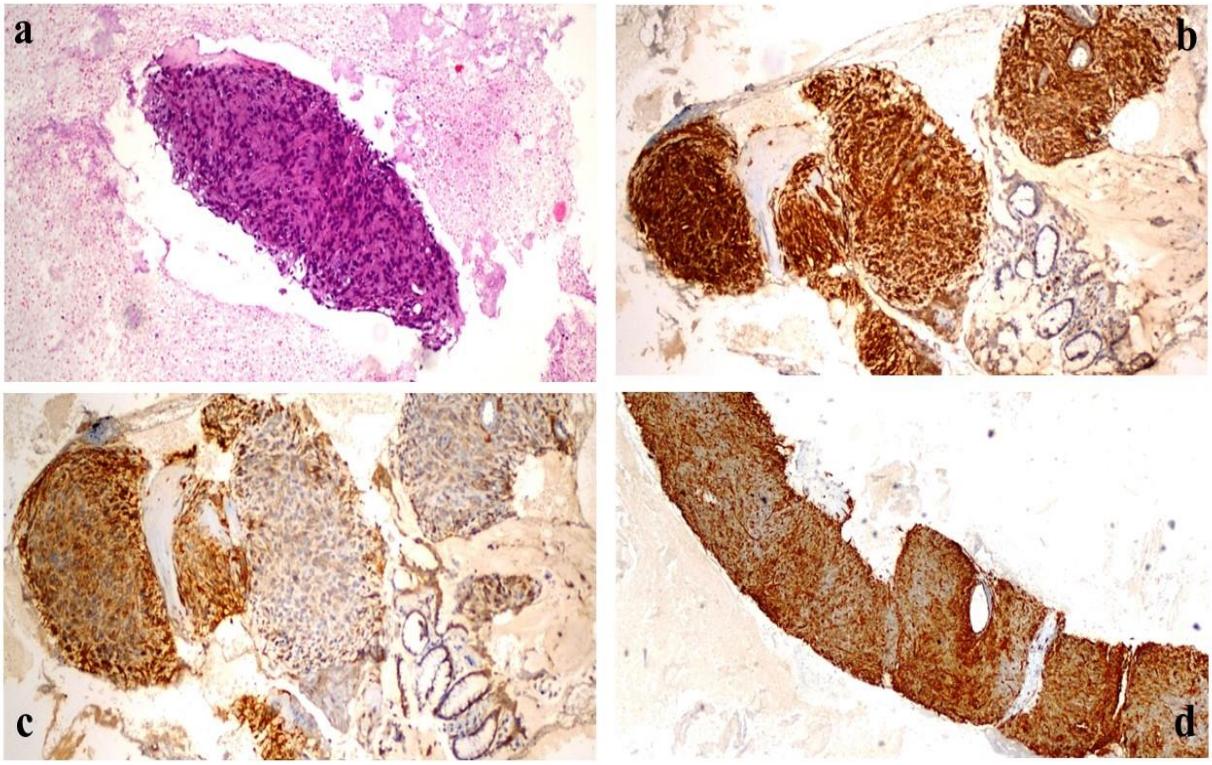

Figure 2. The cell block prepared from ultrasound-guided fine-needle aspiration (EUS-FNA) (a, H&E, x10) showed positive immunstaining with CD117 (b, x10), DOG-1 (c, x10) and CD34 (d, x4).

DISCUSSION

The number of cases may vary due to geographic locations (15). GISTs may occur at any age but there is a tendency to later decades of life (median age 60-65) with a slight predominance of males consistent with our series (2). The most common location for GISTs is the stomach, small bowel, colon, rectum, and esophagus (16). Appendix and extragastrointestinal sites such as omentum, mesentery, and retroperitoneum are rare locations, that consist of less than 5% of all GISTs (2,16). A very small proportion of GISTs may arise within the abdominal cavity and show no apparent connection to any part of the gastrointestinal tract. In such cases entitled extra-gastrointestinal GISTs (10). All of our cases were located in GIS. The symptoms may be vague, mostly bleeding and anemia related to mucosal ulceration. Abdominal pain, discomfort, and new mass may lead to the discovery of the tumor (1,2,3). A variety of symptoms were encountered in our series such as bleeding, abdominal pain, and dyspepsia but interestingly, some tumors were incidentally found during obesity surgery. A careful macroscopic examination of sleeve gastrectomy materials may be helpful in the early detection of GISTs and other tumors.

Since the new immunohistochemical markers are being added to the diagnostic panel of GISTs, CD117 still seems to be the best diagnostic marker. But 5-10% of cases are negative. The staining rates of DOG-1 are very similar to CD117 (17). Unallied of CD117 expression, DOG-1 is a specific and sensitive marker for GISTs. Recently, several studies claimed DOG1 is a more sensitive marker in the diagnosis of GISTs compared to CD117 in both surgical resection materials and cytologic cell blocks (11). CD34 was commonly used in the diagnosis of GISTs before the identification of CD117. But the sensitivity and the specificity of CD34 are low compared to other markers (18). All GIST cases showed positive staining with CD117 in our series. Except for one case, all GISTs were stained with DOG-1. CD34 was negative in six cases. These findings are compatible with the literature and CD34 seems to be less sensitive than CD117 and DOG-1.

Approximately up to 20% of GISTs have metastatic disease at diagnosis (19). The most characteristic sites for GIST metastasis are the abdominal cavity, liver, and lymph nodes. Metastases to lymph nodes are more frequent in pediatric and young adult patients. The lungs, bones, and brain are rare locations for GIST metastasis (10). Three patients had metastatic disease in our series, all three of them were adults with age ranges 38-69. Two cases had liver metastasis and one had metastasis to the regional lymph nodes.

With a variety of classifications from the National Institutes of Health (NIH), AFIP has proposed several criteria to predict prognosis and estimate the potential of malignancy of GISTs, but uncertainty in potential prognostic factors remains (2,19). The most important prognostic factors are tumor size, localization of the tumor, mitotic count, and, tumor rupture (4,19). To count the mitotic figures in 50 hpf, rather than 10 is recommended because GISTs mostly have a low mitotic index (4). Positive surgical margins, tumor necrosis, the genotype of the tumor, and the immune response may also play important role in prognosis. All these parameters were evaluated in this study.

Tumor necrosis is accepted as a significant histopathologic parameter to predict prognosis and recurrence in soft tissue tumors for a long time (20,21). Yi et al. suggested that tumor necrosis may be associated with a poorer prognosis for GISTs in a meta-analysis (19). Recently, many studies reported a variety of possible prognostic factors for GISTs including tumor necrosis, still, the outcomes are controversial (16, 22, 23, 24). The discordance among studies may be associated with small sample sizes such as our study. Liu et al. reported that tumor necrosis has a statistically significant relation with aggressive biological parameters such as nuclear atypia, higher mitotic count, tumor rupture, and larger tumor size (16). In our study, 4 of 6 cases with tumor necrosis were high grade and category 6a and 6b due to AFIP risk criteria.

Yokoi et al. defined new histopathological criteria for assessing the malignant potential of GISTs. The criteria are based on the presence of hemorrhage/ necrosis, tumor size (<5 vs ≥5cm), and ki67 labeling index (<3% vs ≥3%) (24). Based on these criteria, 5 of 6 tumors are malignant with tumor necrosis in our study. When Yokoi's criteria are applied among the GISTs with measurable tumor size, 9 of 23 cases were malignant and, 3 of 9 malignant tumors were low grade with risk category 3a due to AFIP. But there is a consistency among benign cases, 13 of 14 benign GISTs are low grade in our series. Amin et al. categorized GISTs in three groups by combining mitotic count (MC) and tumor size as prognostic parameters: (1) benign: MC less than 5, tumor smaller than 5 cm; (2) borderline: MC less than 5, tumor larger than 5 cm; and (3) malignant: MC greater than 5, tumor any size (25). Due to Amin's category, 13 were benign, 3 were borderline and 7 were malignant in our series. When compared to grade, all benign and borderline GISTs were low grade and all malignant cases were high grade. There is a strong compatibility between grade and Amin's criteria for malignancy in our series.

Miettinen et al. proposed three categories for GISTs as probably benign, probably malignant, and uncertain or low malignant potential based on tumor localization (intestinal or gastric), tumor size, and mitotic count (26). Due to this categorization, 12 were probably benign, 8 were probably malignant and 3 were in the uncertain or low malignant potential category in our series. All of the cases in the probably benign and uncertain or low malignant potential category were low grade, and 7 of 8 cases categorized as probably malign were high grade. These findings favor the common tendency to predict prognosis by tumor size, and mitotic count in GISTs.

The ki67 labeling index is a useful indicator for cell proliferation but yet, but a definite cut-off point for predicting prognosis in GISTs remains unclear. Zhou et al. suggested two cut-off points for ki67. When the ki67 index is higher than 8%, it may predict an unfavorable prognosis (27). Four cases had a higher than 8% ki67 labeling index in our series, They were all high-grade tumors with stages T3 and T4. Two of them had metastases to the liver and lymph nodes. Three of the patients with a high ki67 labeling index passed in 1 to 7 months after diagnosis. These findings support the suggestions about a high ki67 labeling index correlates with an unfavorable prognosis.

Nevertheless, measuring tumor size may not be possible at the time of diagnosis in small endoscopic and fine-needle aspiration biopsies. For submucosal gastric tumors, new safe, and effective biopsy techniques are available. Physicians can provide efficient tumoral tissue for histopathological diagnosis from the submucosal layer with FNA (28). In recent years, new methods such as liquid biopsies started to be used (29). Trindade et al. found endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) is superior to ultrasound-guided fine-needle aspiration (EUS-FNA) for diagnostic efficiency in cases with suspicion of GISTs (30). In our series, 8 of 28 cases were obtained with EUS. Four patients underwent EUS-FNB and 4 patients underwent EUS-FNA. All 8 cases are diagnosed with GIST and samples were efficient to perform immunohistochemistry and diagnostic evaluation.

CONCLUSIONS

In the past years, besides new molecular studies helping us understand the genetic pathway of GISTs, it is also easier to diagnose GISTs with immunohistochemical markers even from minimal tumor tissue obtained with EUS-FNA and EUS-FNBs. Although various studies shared data to define definite prognostic parameters to predict the behavior of GISTs, it remains controversial. In this study, we compared the prognostic and immunohistochemical features of GISTs with the findings of the literature, yet it seems to require more studies in larger series to reveal criteria for understanding the behavior of GISTs.

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RESEARCH ARTICLE

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Epidemiological and Clinical Characteristics of Anterior Shoulder Dislocation Patients in Emergency Departments in Turkey: A Single-Center Experience

ABSTRACT

Objective: This study evaluated the general epidemiological and clinical characteristics of patients admitted to the emergency department with shoulder dislocation.

Methods: This single-center retrospective cross-sectional study, which included patients with anterior shoulder dislocation, was conducted as a chart review at the Emergency Department of the Tekirdag State Hospital between 01 January 2018 to 31 December 2019.

Results: A total of 165 patients (median age 50 years and 60% of males) with anterior shoulder dislocation were included. The most common mechanism was traumatic dislocation (65.5%), the primary reduction technique was traction/countertraction (80.6%). Two-thirds of the patients had right shoulder dislocation, traumatic dislocation, and sedoanalgesia was not required. Age was lower in men, but spontaneous dislocation was more common. The diagnosis was made with an x-ray at a rate of 99%. Emergency physicians were 96% successful.

Conclusions: Direct radiography successfully makes the diagnosis of anterior shoulder dislocation. Anterior dislocation management by emergency physicians is highly successful. It should be considered that atraumatic dislocations are more common in young male patients.

Keywords: Shoulder Dislocation, Anterior Dislocation, Traction, Emergency Department, Turkey.

Türkiye'de Acil Servislerde Ön Omuz Çıkığı Hastalarının Epidemiyolojik ve Klinik Özellikleri: Tek Merkez Deneyimi

ÖZET

Amaç: Bu çalışmada acil servise omuz çıkığı ile başvuran hastaların genel epidemiyolojik ve klinik özellikleri değerlendirildi.

Gereç ve Yöntem: Tek merkezli, retrospektif kesitsel çalışmamızda 01 Ocak 2018 - 31 Aralık 2019 tarihleri arasında Tekirdağ Devlet Hastanesi acil servisinde ön omuz çıkığı olan hastaları incelemesi üzerine yapılmıştır.

Bulgular: Ön omuz çıkığı olan toplam 165 hasta (ortanca yaş 50 ve %60'ı erkekti) dahil edildi. En sık mekanizma travmatik çıkık (%65.5), birincil redüksiyon tekniği traksiyon/ters traksiyon (%80.6) idi. Hastaların üçte ikisinde sağ omuz çıkığı vardı. Ayrıca travmatik çıkıkta vardı ve bunlara sedoanaljezi gerekmedi. Erkeklerde yaş daha gençti ancak spontan çıkık daha yaygındı. Tanı %99 oranında röntgen ile konuldu. Acil servis hekimleri %96 başarılıydı.

Sonuç: Direkt grafi ön omuz çıkığının tanısını başarıyla koyar. Acil hekimleri tarafından anterior çıkık tedavisi oldukça başarılıdır. Atravmatik çıkıkların genç erkek hastalarda daha sık görüldüğü akılda tutulmalıdır.

Anahtar Kelimeler: Omuz Çıkığı, Anterior Çıkık, Traksiyon, Acil Servis, Türkiye

INTRODUCTION

The shoulder is the most common site among all joint dislocations admitted to the emergency department, and the most common shoulder dislocation is an anterior shoulder dislocation (1, 2). Previous studies reported that the overall annual incidence might be as high as 23.9 per 100,000 injuries, or 56.3 per 100,000 individuals per year (2, 3). Although there is no national incidence available, a previous study from Turkey reported a 5.3 per 100,000 person-years, significantly lower than the incidence rates reported for western countries (4). The anatomical characteristics of the glenohumeral joint, which has the greatest range of motion of all joints, also make it the most unstable and vulnerable to dislocation (5). The dislocation mechanism is the removal of the humeral head from joint socket to an anterior direction in almost all cases, which is generally due to a low-energy trauma (6).

Identifying the general epidemiological and clinical characteristics can guide acute management, indication for surgical intervention to prevent recurrence, and education for the patient to re habilitate and reduce longer term morbidity. This is particularly relevant for young male patients with Bankart's lesions who are at very high risk of recurrence without early surgical intervention, implying acute management's importance (7). Therefore, this study evaluated the general epidemiological and clinical characteristics, treatment courses, and outcomes of patients admitted to the emergency department with shoulder dislocations.

MATERIAL AND METHODS

This retrospective cross-sectional study was conducted as a chart review at the Emergency Department of the Tekirdag State Hospital. Patients admitted to the emergency service with a shoulder joint injury between 01 January 2018 to 31 December 2019 were screened from the electronic hospital database system. Patients aged 18 years and older, diagnosed in the emergency department, first reduction performed at the emergency department, and patients with anterior shoulder dislocation were included in the study. The patients with other shoulder dislocations and the first intervention out of the emergency department were excluded from the study. The diagnosis of shoulder dislocation was made by direct radiography or CT. The primary endpoints were epidemiological and clinical characteristics, and the secondary endpoints were patients' treatment characteristics and outcomes as follows:

- **Primary Endpoints:** Age, Gender, Vital signs at admission, Route of entry, Lateralization, Type of dislocation, Mechanism of dislocation
- **Secondary Endpoints:** Pre-reduction and post-reduction imaging modality, Sedoanalgesia, Reduction technique, Practitioner of reduction, Is dislocation recurrent, Presence of simultaneous injury, Post-reduction complication, Length of stay in emergency service, Outcome of treatment in emergency service

Statistical Analyses: Descriptive statistics were presented using median and interquartile range (25th-75th percentiles – IQR) for continuous variables after controlling for normal distribution, and using frequency and percent for categorical variables. In addition, the Mann-Whitney U test and Chi-square test were performed between independent groups for these variables, respectively. A type-1 error level of 5% was considered the statistical significance upper limit ($p<0.05$). All statistical analyses were done in SPSS 25 software (IBM Inc., Armonk, NY, USA).

RESULTS

A total of 165 patients with a median age of 50 years and 60% of males were included in the study. All patients had an anterior dislocation, 54.5% were outpatients, and 64.8% were admitted with dislocation on the right shoulder joint. The most common mechanism was traumatic dislocation (65.5%). The primary diagnostic imaging method was X-Ray both at admission (98.8%) and after reduction (98.2%). One-third of patients received sedation/analgesia, mainly with midazolam (72.7%), and 3.6% received fentanyl. The primary maneuver was traction/countertraction to relocate the affected shoulder in 80.6% of cases, followed by external rotation in 13.3%. An emergency medicine specialist applied the maneuver in 96.4% of cases. Only 1.2% of all patients had a simultaneous humerus fracture. Patients stayed at emergency department for a median of 60 minutes, 99.4% were discharged, and only one patient was hospitalized for further treatment (Table 1).

The comparisons of demographic and clinical data between males and females (Table 2) revealed that males were younger (M/F: median 26/70 years, $p<0.001$), more admitted as outpatients (M/F: 75.8%/22.7%, $p<0.001$), had more spontaneous dislocations (M/F: 46.5%/16.7%, $p<0.001$), received more ketamine (M/F: 8.1%/none) and less propofol (M/F: 1%/9.1%) as sedoanalgesics ($p=0.013$) and stayed less in the emergency department during their treatment (M/F: median [IQR] 60 [40-60]/60 [60-120] minutes, $p<0.001$).

Table 1. Demographic and clinical characteristics of patients with anterior shoulder dislocation

	n (%) / Median [IQR]
Age, years	50 [24-70]
Sex	
Male	99 (60.0)
Female	66 (40.0)
Route of entry	
Ambulance	75 (45.5)
Outpatient	90 (54.5)
Lateralization of dislocation	
Right	107 (64.8)
Left	58 (35.2)
Mechanism of dislocation	
Spontaneous	57 (34.5)
Traumatic	108 (65.5)
Pre-reduction imaging	
Computerized tomography	2 (1.2)
X-Ray	163 (98.8)
Post-reduction imaging	
Computerized tomography	3 (1.8)
Xray	162 (98.2)
Sedation/analgesia	
Administered	55 (33.3)
Ketamine	8 (14.5)
Midazolam	40 (72.7)
Propofol	7 (12.7)
None	110 (66.7)
Reduction technique	
Cunningham	7 (4.2)
External rotation	22 (13.3)
Kocher	1 (0.6)
Stimson	2 (1.2)
Traction/countertraction	133 (80.6)
Practitioner of reduction	
Emergency medicine specialist	159 (96.4)
Orthopedician	6 (3.6)
Length of stay in the emergency department, minutes	60 [60-120]

IQR: Interquartile range

The comparisons of demographic and clinical characteristics of patients according to the mechanism of dislocation are presented in Table 3. Analyses revealed that patients with spontaneous dislocations were younger (median 25 years vs. 61.5 years, $p<0.001$) and predominantly males (80.7% vs. 49.1%, $p<0.001$). Traumatic dislocations were mainly admitted to the emergency department via ambulance services ($p<0.001$). Moreover, spontaneous dislocations tended to be recurrent dislocations when compared to traumatic ones ($p<0.001$), and traumatic dislocations were more associated with spontaneous humerus fractures ($p=0.008$) and stayed at the emergency department for a longer duration ($p<0.001$).

DISCUSSION

Shoulder dislocations are the most common large-joint dislocation presenting to emergency departments, but epidemiological and clinical features of these cases are under investigated in Turkey. Thus, this study evaluated the general demographic and clinical characteristics of these patients. To summarize, our results on an extensive series of cases including 165 patients revealed that the median age was 50 years, and 60% of cases were males. Nevertheless, when the age of patients was evaluated according to sex, males were significantly younger, and median age groups were 2nd and 7th decades for males and females, respectively. Moreover, the mechanism of dislocations was also significantly associated with these baseline demographics that spontaneous dislocations were observed in males and younger ages.

To the best of our knowledge, the epidemiological characteristics of shoulder dislocations in Turkey were only investigated by Tas et al. on 208 cases (8). Authors reported that their patients were mainly males, and peak age groups for males and females were between 21 to 30 years and 61 to 70 years, respectively. The proportion of recurrent dislocations was similar, 22.4% among our cases and 17.3% in the reference study. These background characteristics were in accordance with our results, suggesting a similar pattern of patients in Turkey.

Table 2. Comparisons of demographic and clinical data between genders

	Sex		p
	Male (n=99)	Female (n=66)	
	n (%) / Median [IQR]	n (%) / Median [IQR]	
Age, years	26 [23-47]	70 [62-73]	<0.001
Route of entry			<0.001
Ambulance	24 (24.2)	51 (77.3)	
Outpatient	75 (75.8)	15 (22.7)	
Lateralization of dislocation			0.46
Right	62 (62.6)	45 (68.2)	
Left	37 (37.4)	21 (31.8)	
Mechanism of dislocation			<0.001
Spontaneous	46 (46.5)	11 (16.7)	
Traumatic	53 (53.5)	55 (83.3)	
Pre-reduction imaging			0.52
Computerized tomography	2 (2)	-	
X-Ray	97 (98)	66 (100)	
Post-reduction imaging			0.062
Computerized tomography	-	3 (4.5)	
Xray	99 (100)	63 (95.5)	
Sedation/analgesia			0.013
Ketamine	8 (8.1)	-	
Midazolam	23 (23.2)	17 (25.8)	
Propofol	1 (1)	6 (9.1)	
Fentanyl	4 (4)	2 (3)	
None	63 (63.6)	41 (62.1)	
Reduction technique			0.90
Cunningham	4 (4)	3 (4.5)	
External rotation	14 (14.1)	8 (12.1)	
Kocher	1 (1)	-	
Stimson	2 (2)	-	
Traction/countertraction	78 (78.8)	55 (83.3)	
Practitioner of reduction			0.22
Emergency medicine specialist	97 (98)	62 (93.9)	
Orthopedician	2 (2)	4 (6.1)	
Length of stay in the emergency department, minutes	60 [40-60]	60 [60-120]	<0.001

IQR: Interquartile range

Table 3. Comparisons of demographic and clinical data between spontaneous and traumatic dislocations

	Mechanism of dislocation		p
	Spontaneous (n=57)	Traumatic (n=108)	
	n (%) / Median [IQR]	n (%) / Median [IQR]	
Age, years	25 [23-47]	61.5 [35-72.5]	<0.001
Sex			<0.001
Male	46 (80.7)	53 (49.1)	
Female	11 (19.3)	55 (50.9)	
Route of entry			<0.001
Ambulance	9 (15.8)	66 (61.1)	
Outpatient	48 (84.2)	42 (38.9)	
Lateralization of dislocation			0.084
Right	42 (73.7)	65 (60.2)	
Left	15 (26.3)	43 (39.8)	
Pre-reduction imaging			0.55
Computerized tomography	-	2 (1.9)	
X-Ray	57 (100)	106 (98.1)	
Post-reduction imaging			0.55
Computerized tomography	-	3 (2.8)	
Xray	57 (100)	105 (97.2)	
Sedation/analgesia			0.88
Ketamine	2 (3.5)	6 (5.6)	
Midazolam	16 (28.1)	24 (22.2)	
Propofol	3 (5.3)	4 (3.7)	
Fentanyl	2 (3.5)	4 (3.7)	
None	34 (59.6)	70 (64.8)	
Reduction technique			0.22
Cunningham	1 (1.8)	6 (5.6)	
External rotation	6 (10.5)	16 (14.8)	
Kocher	-	1 (0.9)	
Stimson	2 (3.5)	-	
Traction/countertraction	48 (84.2)	85 (78.7)	
Practitioner of reduction			0.094
Emergency medicine specialist	57 (100)	102 (94.4)	
Orthopedician	-	6 (5.6)	
Length of stay in the emergency department, minutes	60 [40-60]	60 [60-120]	<0.001

IQR: Interquartile range

The difference between the two studies was that 94.3% of their cases had anterior dislocations, and relocation was made in the emergency department in 79.3% of patients, whereas all patients in our study had an anterior dislocation and 96.4% of them were relocated in the emergency department in our study.

The international studies that evaluated these characteristics also reported different results which might be associated with the population-specific features. For example, Liavaag et al. (3) studied the epidemiological characteristics of shoulder dislocations in Oslo, Norway. They reported that primary dislocations formed 46.6% and recurrent dislocations 41.4% of total cases, which is significantly higher for recurrent dislocations than in our study. The ages of males and females were also slightly different, median 34 and 54 years, respectively, which is notably higher for males than our results. Another study from Sweden by Nordqvist et al. (9) reported median ages of 44 and 63 for males and females in shoulder injuries, respectively, which is also significantly higher for males than our findings. These differences suggest that shoulder dislocations are seen at younger ages among males in Turkey.

The mechanism of shoulder dislocation was evaluated extensively in the literature. The primary etiology in young males was reported to be contact sports (10). The excess external rotation in abduction impulses the humeral head out of the socket and avulses the anterior structures of the glenoid, also classified as the Bankart lesion. Then, the posterior humeral head exits the joint and forms an indentation called the Hill Sachs lesion when positioned in line with the anterior rim of the glenoid (11). This type of dislocation is typically diagnosed with X-Ray, the first-choice imaging method for traumatic shoulder pathologies (12). Our results showed that this is also the case among our cases, in which almost all patients were diagnosed, and the relocations were confirmed by X-Ray imaging. Nevertheless, up to 60% of bone lesions may not be identified by the X-Ray, and computerized tomography emerges as the preferred method for these cases (13). But, only less than 2% of our patients needed further imaging with computerized tomography, which implies the importance of X-Ray for shoulder dislocations.

The primary treatment of anterior shoulder dislocation is the reduction of the humerus head. The literature data on this revealed that the most frequent maneuvers for reduction are traction/countertraction, Kocher, Cunningham, Stimson plus scapular manipulation, and external rotation plus Milch methods (1, 14). The primary maneuver for reduction among our cases was traction/countertraction in 80.6% of cases, followed by external rotation in 13.3%. The traction-counter traction maneuver is applied when a physician pulls the dislocated arm in 45□ abduction and external rotation position, while another pulls the patient's chest in the counter direction. This traction and countertraction are best applied when two sheets or towels are wrapped on the chest and tied to the elbow of dislocated arm for pulling in opposite directions. And, for the external rotation method, there is still debate on whether it is better than internal rotation or not. Some authors reported that these strategies provide similar outcomes (15,16), but several others reported that external rotation is associated with lower recurrence (17).

As a consequence, the experience and expertise of the physician seemed to be deterministic of the best method to apply. Also, apart from the maneuver of choice for treatments, adequate analgesia is another determinant of successful reduction. About one-third of our patients received sedoanalgesia, primarily with midazolam, and 3.6% received fentanyl. The effectiveness of analgesia before the reduction was evaluated in several previous studies. For example, Taylor et al. (18) compared propofol and midazolam and reported that propofol was as effective as midazolam/fentanyl and associated with better muscle relaxation. There are also other studies conducted with different agents or administration routes like intraarticular injections, suprascapular nerve blocks, etc. (19-21), which all can be concluded as that the effectiveness is important when only considered along with the expertise of the physician administering the reduction maneuver appropriately (22).

The choice of technique should be informed by the subtype of anterior shoulder dislocation. Kocher, Cunningham and external rotation maneuvers are designed to be used in subcoracoid dislocations and are not well suited to subglenoid dislocations. This means that even for an experienced practitioner, the wrong choice of technique may result in an unsuccessful attempt, or excessive use of analgesia/sedation, or the incorrect application of traction.

This study is the first case review to analyze the incidence of anterior shoulder injury subtypes and the appropriateness of applied techniques in the emergency departments in Turkey. The main limitation of the study is that the subtypes of the dislocations were not adequately detailed in the reports, meaning that there is limited understanding of the importance of injury subtype in the assessment and subsequent technique choice in shoulder dislocations. Nevertheless, the data presented and the limitations underlined in this study may enhance the clinical practices regarding the management of shoulder dislocations in emergency departments.

CONCLUSION

Epidemiological data on shoulder dislocation in Turkey is scarce. This is the second study that provides recent evidence on the demographic and clinical characteristics of these patients as well as the treatment methods and outcomes of these cases in emergency departments Direct radiography successfully makes the diagnosis of anterior shoulder dislocation. Anterior dislocation management by emergency physicians is highly successful. It should be considered that atraumatic dislocations are more common in young male patients. Further studies evaluating the incidence and long-term follow-up data are also needed to better elucidate epidemiological features and clinical interventions' effectiveness.

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RESEARCH ARTICLE

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The Evaluation of Relationship between Monocyte/High-Density Lipoprotein Ratio (MHR) and COVID-19

ABSTRACT

Objective: Early diagnosis is important for severe diseases in COVID-19. Monocyte/high dansity lipoprotein ratio (MHR) is a new prognostic marker indicating inflammation. We aimed to investigate the relationship between MHR and diseases severity in COVID-19.

Methods: Patients with laboratory confirmed COVID-19, were retrospectively analyzed. Clinical symptoms, signs and laboratory data on the first day of hospitalization were obtained from medical records of hospital. The clinical data of 301 patients were included in study. Cases were diagnosed on the basis of interim guidance of World Health Organization (WHO). Patients were classified into two groups as non-severe COVID-19 and severe COVID-19. MHR were calculated with laboratory data on the first day of hospitalization. The relationship between MHR level and COVID-19 severity was evaluated. Statistical analysis of the data was performed by using SPSS 25 (SPSS Inc., Chicago, IL, USA) package program. Statistical significance level was accepted as $p<0.05$.

Results: One hundred ninety-six patients (65.1 %) had non-severe COVID-19,105 patients (34.9 %) had severe COVID-19. In our study, it was found that the mean age was higher in severe patients and comorbid diseases were more common. Although monocyte count values were not statistically significantly different, MHR was significantly higher in severe COVID-19 than non-severe COVID-19.

Conclusions: Monocytes are very important to cytokine storm in COVID-19. Dyslipidemia can occur in viral infection because of inflammation. MHR can be used as an inflammatory marker in COVID-19.

Keywords: COVID-19, High-Density lipoprotein, Inflammation, Monocyte, Severe Diseases.

Monosit/ Yüksek Dansiteli Lipoprotein (MHR) ve COVİD-19 Arasındaki İlişkinin Değerlendirilmesi

ÖZET

Amaç: COVID-19'da şiddetli hastalığı erken tanımak önemlidir. Monosit / yüksek dansiteli lipoprotein oranı (MHR), inflamasyon seyrini belirlemede kullanılan yeni bir belirteçtir. Bu çalışmada MHR ile COVID-19 seyri arasındaki ilişkiyi incelemek amaçlanmıştır.

Gereç ve Yöntem: Laboratuvar ile konfirme edilmiş COVID-19 hastaları retrospektif olarak analiz edildi. Hastanemize başvuran hastanın ilk günki klinik semptomları, bulguları ve laboratuvar sonuçları hastane bilgi işlem sisteminden taranarak kayıt altına alındı. Çalışmamıza toplam 301 hasta dahil edildi. Hastalar Dünya Sağlık Örgütü (DSÖ) klavuzu dikkate alınarak sınıflandırıldı. MHR hastaların hastaneye kabul edildiği ilk gün bakılan laboratuvar verileri kullanılarak hesaplandı. MHR ile COVID-19 şiddeti arasındaki ilişki değerlendirildi. Hasta verileri SPSS 25 (SPSS Inc., Chicago, IL, USA) kullanılarak analiz edildi. İstatistiksel olarak $P<0.05$ olan farklılıklar anlamlı kabul edildi.

Bulgular: Hastaların 196 (%65,1)'sı hafif ve orta semptomlu COVID-19 iken, 105 (%34,9)'i şiddetli COVID-19 idi. Çalışmamızda şiddetli COVID-19 hastalarında yaş ortalamasının daha yüksek olduğu ve komorbid hastalıkların daha sık görüldüğü bulunmuştur. Çalışmamızda grublar arasında monosit sayısında anlamlı fark izlenmez iken, şiddetli COVID-19 hasta grubunda MHR anlamlı olarak daha yüksek saptanmıştır.

Sonuç: COVID-19'da gerçekleşen sitokin fırtınasında monositler önemli rol üstlenir. Gelişen inflamasyon nedeni ile hastalarda dislipidemi izlenir. MHR COVID-19'da inflamatuar biyobelirteç olarak kullanılabilir.

Anahtar Kelimeler: COVID-19, Yüksek dansiteli lipoprotein, İnflamasyon, Monosit, Şiddetli Hastalık

INTRODUCTION

In December 2019, cases of pneumonia with unknown etiology have been reported in Wuhan, China (1). On February 11 2020, the Word Health Organization (WHO) named the pneumonia with unknown etiology as coronavirus disease 2019 (COVID-19). On March 11 2020, first case of COVID-19 has been reported in Turkey. Clinical features and risk factors are highly variable. For patients with a non-severe diseases of COVID-19, clinical symptoms are fever, cough, fatigue and pneumonia. For patients with severe diseases of COVID-19, acute respiratory distress syndrome (ARDS) and organ failure may develop (2-4). Some patients with pneumonia may progress rapidly and may need mechanical ventilation. Mortality rate for these patients is quite high even reaching a level of 60 % (5). Early diagnosis and early treatment are very important especially for severe disease.

Immune response of severe patients may cause macrophage-activation syndrome (MAS). Low expression of HLA-DR on CD14 monocytes causes immune dysregulation. Immune dysregulation is triggered by monocyte hyperactivation, releases of interleukin-6 (IL-6), and profound lymphopenia. This immune response is different from in either ARDS caused by 2009 H1N1 influenza or bacterial sepsis (6).

Lipids are very important for viral infections such as human immunodeficiency virus (7). High-density lipoprotein cholesterol (HDL-C) has got an immunregulatory effect. It has anti-inflamatory and anti-oxidant effects (8).

Inflammation is very important for the progression of COVID-19. So inflammation biomarkers can be used to determine prognosis of COVID-19 patients (9). The ratio of monocyte count to the HDL-C level (MHR) was used to determine oxidative stress and inflammation (8, 10). MHR is one of the indicators of systematic inflammatory response. Therefore, we aimed to investigate the relationship between MHR and COVID-19 diseases.

MATERIAL AND METHODS

Patients: Patients with laboratory confirmed COVID-19 who were admitted to the hospital, between March 11 2020 and April 30 2020, were retrospectively screened. Patients with COVID-19 were confirmed by a positive result from real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay with nasal and pharyngeal swab specimens for SARS-CoV-2 RNA (Bio-speedy COVID-19 RT-qPCR test kit). The clinical data of 380 patients have been obtained. Patients who were under the age of 18, pregnant, using steroid therapy, who had malignancy, hyperlipidemia and hematological diseases were excluded. A total of 301 patients were included in the final analysis. Cases were diagnosed on the basis of interim guidance of WHO (11). Patients have got positive results of RT-PCR for SARS-CoV-2, were classified into two groups as non-severe disease and severe diseases. A respiratory rate ≥30 and an oxygen saturation (resting state) ≤93 on room air were accepted for severe diseases.

The endpoint of follow up was the admission to the intensive care unit, discharge or cure. This study was approved by Locals Ethics committee (day: 21.05.2020 , number: E1-20-624)

Clinical Characteristics and Laboratory Data: Clinical symptoms, signs and laboratory data were obtained from medical records of hospital. Blood samples were taken from patients on the first day of admission. Laboratory assessments consisted of complete blood count, blood lipid profiles, blood chemistry, coagulation tests (D-dimer, prothrombin time (PT), activated partial prothrombin time (aPTT), international normalized ratio(INR), thrombin time(TT)), C-reaktive protein (CRP) levels, procalcitonin (PCT). MHR was calculated as the ratio of the monocyte count to the level of HDL-C.

Statistical Analysis: Statistical analysis of the data was performed by using SPSS 25 (SPSS Inc., Chicago, IL, USA) package program. The normal distribution of the data was tested with the Shapiro-Wilk test. Descriptive statistics of categorical variables were reported as numbers and percentages (%). Descriptive statistics of continuous variables were presented with mean±standard deviation (SD) and median (min-max) according to data normality distribution. The relationships between severity of COVID-19 and sociodemographic characteristics, comorbidity status, were performed using Chi-square test or Fisher's exact test in accordance with the number of data in crosstab cells. Statistical significance level was accepted as $p<0.05$.

RESULTS

Three hundred and one patients were included in the study. Comparison of demographic, comorbidity status of patients and patient outcome between study groups were presented in table 1. One hundred and twenty one (65.2 %) of patients were women and 105 (34.8 %) were men. There was no statistically difference for gender distribution between study groups ($p = 0.033$, Table 1). The mean age was 42.48 ± 15.24 in non-severe diseases. The mean age was 64.35 ± 13.06 in severe diseases. Ages of patients were statistically different between groups ($p < 0.001$). One hundred ninety six patients (65.1 %) had non-severe disease, 105 patients (34.9 %) had severe diseases.

The mean length of stay at intensive care unit (ICU) in the severe group was 7 (0-41) days. The length of hospital stay of patients with severe diseases was 15 (4-52) days. The length of hospital

stay and length of stay at ICU was significantly different between groups (p <0.001). Comorbidities (Coronary artery disease, hypertension (HT), diabetes mellitus (DM), chronic lung disease, chronic kidney disease) were statistically different between study groups (Table 1).

Table 1. Comparison of demographic, comorbidity status of patients and patient outcome between research groups

		Groups		*P* values
		Non-Severe (n=196)	**Severe (n=105)**	
Gender	Male n (%)	100(51%)	70(63.6%)	0,033
Age Mean (+/- SD)		42.48 +/- 15.24	64.35 +/- 13.06	<0.001
Coronary Artery Disease		8 (4.1%)	18 (17.1%)	<0.001
HT		27 (13.8%)	41 (39.0%)	<0.001
DM		16 (8.2%)	33 (31.4%)	<0.001
Chronic Lung Disease		11 (5.6%)	21 (20.0%)	<0.001
Chronic Kidney Disease		3 (1.5%)	9 (8.6%)	0.005
Intensive Care Unit Status		0 (0%)	32 (30,5%)	<0.001
Mechanical Ventilation		0 (0%)	8 (7.6%)	<0.001
Mortality		0 (0%)	16 (15.2%)	<0.001

In the severe groups, 30.5% of patients were admitted to ICU and 7.6% needed mechanical ventilation.

The comparison of laboratory blood values between research groups is given in Table 2. Although monocyte count values were not statistically significantly different, MHR was significantly different between the groups. MHR level was higher in the severe groups than in the non-severe groups. White blood cell (WBC), neutrophil, lymphocyte, neutropil-to-lymphocyte ratio (NLR), HDL-C, hemoglobin, creatinine, glomerular filtration rate (GFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, CRP, procalcitonin (PCT), troponin, total cholesterol (TC), triglyceride (TG), PT, INR, ferritin, D-dimer and fibrinojen values were significantly different between the study groups (Table 2).

Table 2. Comparison of clinical laboratory values between research groups

	Groups		*P* values
	Non-Severe (n=196)	**Severe (n=105)**	
WBC	4755 (1450-16180)	7320 (3030-19730)	<0.001
Neutrophil	2855 (200-12810)	6110 (2290-18550)	<0.001
Lymphocyte	1270 (186-7360)	640 (260-2190)	<0.001
NLR	2.095 (0-15)	9.600 (1.9-42.2)	<0.001
Monocytes	360 (100-1670)	360 (60-1530)	0.53
HDL	37 (20-98)	28 (11-66)	<0.001
MHR	9.7 (2.4-31.1)	11.3 (1.6-34.8)	<0.015
Hemoglobin	13.8 (9.5-17)	13.1 (7.9-16.8)	<0.001
PLT	215500 (75000-451000)	226000 (31000-591000)	0.044
Creatinine	0.8(0-2)	0.92 (0-5)	<0.001
GFR	103.5(26-148)	78 (9-123)	<0.001
AST	23 (4-166)	41 (15-500)	<0.001
ALT	27 (7-248)	34 (9-634)	<0.001
Total bilirubin	0.5 (0.1-4)	0.5 (0.2-1.9)	0.051
Albumin	45 (36-54)	38 (21-47)	<0.001
CK	100 (12-1186)	123 (15-5395)	0.053
LDH	210.5 (40-551)	372 (45-1000)	<0.001
CRP (g/L)	0.005 (0.001-0.168)	66 (0.001-258)	<0.001
PCT	0.03 (0.01-0.79)	0.11 (0.01-9.7)	<0.001
Troponin	2.5 (0.01-5033)	8 (1-25000)	<0.001
Total Cholesterol	150 (45-318)	140 (61-351)	0.041
LDL	91 (4-270)	83 (26-240)	0.081
TG	99 (10-591)	124 (16-313)	<0.001
PT	12 (10-48)	12.7 (10-44.3)	<0.001
aPTT	24.6 (19.7-95.6)	25 (16.7-49.5)	0.866
INR	1 (0.89-4.40)	1.08 (0.8-4.03)	<0.001
Ferritin	100 (1-1448)	431 (17-2131)	<0.001
D-Dimer	0.32 (0.1-35.2)	0.9 (0.1-35.2)	<0.001
Fibrinogen	2.92 (1.32-7.01)	5.9 (2.2-10.1)	<0.001
Length Of Hospital Stay	10 (2-31)	15 (4-52)	<0.001
Length Of Intensive Stay	0	7 (0-41)	<0.001

DISCUSSION

Most people with COVID-19 develop mild illness. Rate of severe disease development is 14%. And 5% of severe diseases patients require admission to an intensive care unit (ICU) (11). The risk factors associated with disease severity were reported as DM, increased age and organ failure (12-14). Early diagnosis and early treatment is very important for decrease the mortality. It is as important to evaluate laboratory tests as to know the risk groups to know severe patients early. In various studies, some laboratory parameters such as WBC,neutrophil count, lymphocytes count, NLR, creatinine, AST, ALT, CRP, PCT, D-dimer, ferritin were found to be significantly different for severe disease,as in our study (16-18). Could MHR be a new inflammatory marker for COVID-19?

MHR is a new inflammatory marker for several diseases such as cardiovascular diseases.

In this study, count of monocytes was not significantly different between severe and non severe diseases. Some studies showed that, in the severe ICU group, severe non-ICU group and common group were compared. There is not statistically significant difference between the study groups in the number of monocytes (17). Monocytes are cells of the innate immune system are participating in inflammatory response, phagocytosis and antigen presentation. Three types of monocytes are classified according to their CD14 and CD16 expression. These are classical (CD14+, CD16-), intermediate (CD14+, CD16+) and non-classical (CD14dim CD16+) (19). Intermediate monocytes significantly increase in patients with COVID-19. The rate which is 5% of total monocyte in the healthy population increases to over 45% in patients with COVID-19. These monocytes are producing interleukin-6 (IL-6) (20). So that, monocytes are very important to cytokine storm in COVID-19. We couldn't assess monocyte subtypes and IL-6 levels in our study population. This was a limitation of our study.

Dyslipidemia is one of the outcome of inflammation in viral infections (21). SARS-CoV-2 is an enveloped virus surrounded by a lipid bilayer, with a genome of 30.000 nucleotides, encoding four structural proteins. These are nucleocapsid (N) protein, spike (S) protein, nucleocapsid (N) protein, envelope (E) protein and membrane (M) protein (22). Lipids main components of SARS-CoV-2, are involved in fusion of viral membrane to host cell, viral replication, endocytosis and exocytosis. Cholesterol and lipid raft play a key role especially in the early stage of cell infection. Low levels of TC, HDL-C and LDL-C are associated with disease severity and mortality (23). In our study TC, HDL-C, and LDL-C levels decreased, TG levels increases in correlation with disease severity. HDL-C has got protective effects against lipid oxidation. So it is called an anti-inflammatory lipoprotein. HDL-C negatively regulate expression of inflammatory mediators and T-cells activation in dendritic cells and macrophage (15). HDL-C has a protective role in the inflammation effect on the lungs. Described HDL-C level is useful in predicting the severity of COVID-19 disease (24). As the severity of the disease increases, the decrease in the lipid level is exacerbated (25).

In this study, the MHR increased in correlation with disease severity. High MHR may be correlated with a poor prognosis for COVID-19 patients. The further studies with larger patient groups will be beneficial for understanding the relationship between MHR and COVID-19.

Study Limitations: The first limitation of our study is our study sample groups is small. We couldn't assess monocyte subtypes and IL-6 levels in our study population. This was second limitation of our study. The third limitation is the not performing a multivariant analysis. We need advanced studies to determine ıf MHR is an independent risk factor. And we can determine a cut off value of MHR for severe COVID-19 disease.

CONCLUSION

COVID-19 courses are highly variable. So biomarkers are very important to recognize serious disease early. MHR is an important marker for inflammation. MHR can be one of these markers to determine COVID-19 severity. High MHR is correled with the severity of disease ın our study. MHR needs a lot of study with more patients to explore the importance of COVID-19. If researcher can be determine a cut off value of MHR, it can be used as an inflammatory marker in COVID-19 as in cardiovascular diseases.

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RESEARCH ARTICLE

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Lifelong Learning Tendencies of Faculty of Medicine Students

ABSTRACT

Objective: The aim of this study is to determine the lifelong learning tendencies of the students studying at the medical faculty and whether there is a relationship between lifelong learning tendencies and gender, grade level variables.

Methods: In the study, "Lifelong Learning Tendency Scale", sociodemographic question form were applied face to face to the medical faculty students (n= 196) in the 2019-2020 academic year. Statistical evaluation was made with the SPSS statistical program. Mean, standard deviation, frequency, percentage, Mann Whitney U, Kruskall Wallis tests were applied.

Results: Means of motivation, persistence, deprivation in regulating learning, deprivation in curiosity subdimensions, total score average are 6.43 + 2.43; 18.9 + 6.23; 24.48 + 5.05; 24.5 + 6.54; 74.34 + 9.56 respectively. The mean levels of females in motivation and deprivation in regulating learning were significantly lower than males; males' total score mean was significantly higher than females ($p<0.05$). Fifth grade students' deprivation in regulating learning averages were significantly higher than the first grade ($p= 0.001$). Fifth grade students' deprivation in regulating learning averages were significantly higher than the second grade ($p= 0.039$). Fifth grade students' deprivation in regulating learning mean was significantly higher than the third grade ($p=0.017$). Fourth grade students' lifelong learning tendencies total score was significantly higher than the first grade ($p= 0.013$). Fifth grade students' lifelong learning tendencies total score was significantly higher than the first grade ($p= 0.012$).

Conclusions: Appropriate environments should be prepared to increase the lifelong learning tendencies of medical faculty students. In this direction, on-campus and off-campus systems should be developed in which students can easily access and effectively use learning resources.

Keywords: Lifelong Learning, Tendency, Faculty, Medicine, Student.

Tıp Fakültesi Öğrencilerinin Yaşam Boyu Öğrenme Eğilimleri

ÖZET

Amaç: Bu çalışmanın amacı tıp fakültesinde eğitim gören öğrencilerin yaşam boyu öğrenme eğilimlerini ve yaşam boyu öğrenme eğilimleri ile cinsiyet ve sınıf düzeyi değişkenleri arasında bir ilişki olup olmadığını belirlemektir.

Gereç ve Yöntem: Araştırmada, 2019-2020 eğitim öğretim yılında tıp fakültesi öğrencilerine (n= 196) "Yaşam Boyu Öğrenme Eğilimi Ölçeği" ve sosyodemografik sorulardan oluşan form yüz yüze uygulanmıştır. İstatistiksel değerlendirme SPSS istatistik programı ile yapılmıştır. Ortalama, standart sapma, sıklık, yüzde, Mann Whitney U, Kruskall Wallis testleri uygulanmıştır.

Bulgular: Motivasyon, sebat, öğrenmeyi düzenlemede yoksunluk, merak yoksunluğu alt boyut ortalamaları, toplam puan ortalaması sırasıyla 6,43 + 2,43; 18,9 + 6,23; 24,48 + 5,05; 24,5 + 6,54; 74,34 + 9,56'dır. Kadınların motivasyon ve öğrenmeyi düzenlemede yoksunluk ortalamalarının erkeklere göre anlamlı olarak daha düşük; erkeklerin toplam puan ortalamalarının kadınlara göre anlamlı olarak daha yüksek olduğu belirlenmiştir ($p<0.05$). 5.sınıf öğrencilerinin öğrenmeyi düzenlemede yoksunluk ortalamalarının 1.sınıfa göre anlamlı olarak daha yüksek ($p= 0.001$), 5.sınıf öğrencilerinin öğrenmeyi düzenlemede yoksunluk ortalamalarının 2.sınıfa göre anlamlı olarak daha yüksek ($p= 0.039$), 5.sınıf öğrencilerinin öğrenmeyi düzenlemede yoksunluk ortalamalarının 3.sınıfa göre anlamlı olarak daha yüksek ($p=0.017$) olduğu saptanmıştır. 4.sınıf öğrencilerinin yaşam boyu öğrenme eğilimleri toplam puanının 1.sınıfa göre anlamlı olarak daha yüksek ($p= 0.013$), 5.sınıf öğrencilerinin yaşam boyu öğrenme eğilimleri toplam puanının 1.sınıfa göre anlamlı olarak daha yüksek ($p= 0.012$) olduğu saptanmıştır.

Sonuç: Tıp fakültesi öğrencilerinin yaşam boyu öğrenme eğilimlerinin arttırılmasına yönelik uygun ortamlar hazırlanmalıdır. Bu doğrultuda öğrencilerin öğrenme kaynaklarına kolayca erişebileceği ve etkin biçimde kullanacakları kampüs içi ve dışı sistemler geliştirilmelidir.

Anahtar Kelimeler: Yaşam Boyu Öğrenme, Eğilim, Fakülte, Tıp, Öğrenci.

INTRODUCTION

In the twenty-first century, the context of learning has changed to meet life-related needs. It has come to the fore not to transfer past information to students, but to gain the skills of accessing updated information in the fastest and most reliable ways and using this information appropriately. The understanding of "education and learning" that continues throughout adulthood and/or vocational education has evolved into a "lifelong education and learning" approach (1). Technological developments and scientific studies have rapidly developed communication tools and these tools have enabled everyone to reach this information. In our world where such rapid changes are experienced, knowledge assumes the position of the main source of production and development. Therefore, accessing, using and producing information has become the social and economic necessities of the age (2).

Lifelong learning was first used by Grundtvig (3) and came to the education in 1970 (4). Lifelong learning is defined as the educational process that takes place throughout life without restrictions (5). Lifelong learning is all kinds of formal, non-formal or distance education that individuals receive as a result of their needs in order to enable them to gain new knowledge and skills at any stage of their lives without limitation of time, place and subject, or to improve their existing knowledge and skills (6). Lifelong learning is when individuals have the knowledge and skills necessary for self-learning without the need for anyone else. It should be aimed to train students who are responsible for and can manage their own learning (7).

The rapid change that is happening day by day in today's society makes it necessary for individuals to constantly renew / improve themselves. Thanks to today's possibilities, the individual can create a self-learning environment by making use of various tools and equipment. In addition, many types of education such as e-learning, distance education, courses, in-service, pre-service, vocational and technical education are included at the scope of lifelong learning (8).

Considering the definitions made in the literature, the focus in lifelong learning is individual's continuous self-improvement. This concept includes continuity of learning and four different components: motivation, persistence, curiosity and self-regulation (9).

It is very important to determine the lifelong learning tendencies of medical faculty students in order to increase the lifelong learning skills. The aim of this study is to determine lifelong learning tendencies of medical faculty students and whether there is a relationship between lifelong learning tendencies and gender, grade variables.

MATERIAL AND METHODS

In the study "Lifelong Learning Disposition Scale" was used. This scale was developed by Coşkun (10) on university students and validity and reliability study was conducted for the field of medical education by Arslan et al. (1). This scale consists of 25 items and four subdimensions. The dimensions are: Motivation (4 items), persistence (8 items), deprivation in regulating learning (5 items) and deprivation in curiosity (8 items). The Cronbach's alpha +of the scale was 0.92 (1).

In this study, stratified sampling method was used. Students are stratified by each grade and gender. The sample volume was calculated as follows: According to the literature (9), students' lifelong learning tendency scale score was taken as 89.09±15.28 to find a 5% difference significant with 0.01 probability of error and 90% power it was calculated that 179 cases should be taken. However, considering possible case losses, it was decided to recruit 200 students. In the study, 98% (n=196) of 200 students were reached. In the study, lifelong learning tendencies scale and sociodemographic questions were applied face to face to medical school students (n = 196) in the 2019-2020 academic year.

Statistical evaluation was made with the SPSS statistics program. Mean, standard deviation, frequency, percentage, Mann Whitney U and Kruskall Wallis tests were used. The results were interpreted at a 95% confidence interval, with a significance level of $p < 0.05$.

In the study, scale's Cronbach's alpha was 0.884, and the Cronbach's alpha values of the sub-dimensions of motivation, persistence, lack of regulation of learning, lack of curiosity were 0.689, 0.808, 0.693, 0.795 respectively.

Ethics committee approval was received from Trakya University Faculty of Medicine Scientific Research Ethics Committee (Decision No: 14/14, Date: 02.09.2019).

RESULTS

Motivation subscale mean was 6.43 ± 2.43; Persistence subscale mean was 18.9 ± 6.23; Deprivation in regulating learning subscale mean was 24,48 ± 5,05; The mean of deprivation in curiosity subscale was 24.5 ± 6.54. The total score average was 74.34 ± 9.56.

In Table 1, the distribution of students according to gender and grade level is seen.

Table 1. Distribution of students according to gender and grade

VARIABLES	**n**	**%**
Gender		
Female	111	56.6
Male	85	43.4
Grade	**n**	**%**
First	50	25.5
Second	33	16.8
Third	41	20.9
Fourth	20	10.2
Fifth	52	26.5
TOTAL	196	100.0

As seen in Table 2, females' motivation and deprivation in regulating learning averages were significantly lower than males ($p < 0.05$). The total mean scores of males were significantly higher ($p < 0.05$) than females.

As seen in Table 3, it was determined that the average of deprivation in regulating learning and total score averages differ significantly ($p < 0.05$) according to grade.

Table 2. Comparison of lifelong learning tendencies subdimension averages according to gender

VARIABLES	Gender	N	Mean Rank	Mann Whitney U	p
Motivation	Female	111	87.20	3463.000	**0.001**
	Male	85	113.26		
Persistence	Female	111	92.64	4066.500	0.097
	Male	85	106.16		
Deprivation in regulating learning	Female	111	89.19	3684.000	**0.008**
	Male	85	110.66		
Deprivation in curiosity	Female	111	91.62	3953.500	0.052
	Male	85	107.49		
Total score	Female	111	89.00	3663.000	**0.007**
	Male	85	110.91		

Table 3. Comparison of lifelong learning tendencies subdimension averages according to grade

VARIABLES	Grade	N	Mean Rank	X^2	p
Motivation	First	50	93.25	1.530	0.821
	Second	33	107.44		
	Third	41	96.73		
	Fourth	20	94.38		
	Fifth	52	100.86		
Persistence	First	50	86.80	5.006	0.287
	Second	33	94.17		
	Third	41	97.72		
	Fourth	20	104.68		
	Fifth	52	110.74		
Deprivation in regulating learning	First	50	80.74	13.658	**0.008**
	Second	33	93.61		
	Third	41	92.05		
	Fourth	20	109.93		
	Fifth	52	119.38		
Deprivation in curiosity	First	50	88.25	8.969	0.062
	Second	33	87.08		
	Third	41	99.45		
	Fourth	20	128.50		
	Fifth	52	103.32		
Total score	First	50	83.13	10.072	**0.039**
	Second	33	91.52		
	Third	41	95.07		
	Fourth	20	118.38		
	Fifth	52	112.77		

Fifth grade students' average deprivation in regulating learning was significantly higher than the first grade students (Mann Whitney U = 801.000; p = 0.001).

The average deprivation in regulating learning of fifth grade students was significantly higher than the second grade students (Mann Whitney U = 629.500; p = 0.039).

Fifth grade students' deprivation in regulating learning average was significantly higher than the third grade (Mann Whitney U = 759.500; p = 0.017).

The total score of fourth grade students' lifelong learning tendencies was significantly higher than the first grade students (Mann Whitney U = 310.000; p = 0.013).

The total score of fifth grade students' lifelong learning tendencies was significantly higher than the first grade students (Mann Whitney U = 927.000; p = 0.012).

DISCUSSION

In our study, mean of motivation subdimension was 6.43 $\pm$ 2.43; mean of persistence subdimension was 18.9 $\pm$ 6.23; mean of deprivation

in regulating learning subdimension was 24.48 ± 5.05; mean of the deprivation in curiosity sub-dimension was 24.5 ± 6.54. The total score average was 74.34 ± 9.56. Female students' motivation and deprivation in regulating learning averages were significantly lower than males ($p < 0.05$). The total mean scores of males were significantly higher ($p < 0.05$) than females.

In the literature, there are research results that parallel and differ from the findings obtained in our study. In a study, male students' lack of curiosity sub-dimension scores were higher than female students. Students' motivation, persistence, deprivation in regulating learning and total scores didn't differ significantly according to gender (4). Şahin et al. (11) and Kangalgil and Özgül (12) found that lifelong learning of students didn't differ according to gender. In some studies, female students have higher lifelong learning tendencies than male students (9,13,14,15,16). In the study of Gencel (13), female students' perceptions of lifelong learning competencies were significantly higher than male students.

In our study, lifelong learning tendency total score average was 74.34 ± 9.56. In a study students' lifelong learning tendencies were low (4). Similarly, in a study conducted by Coşkun and Demirel (9), students' lifelong learning tendencies were low. In a study conducted with nursing students, the average score of Lifelong Learning Tendencies Scale was 68.1 ± 23.58 (17). In another study, lifelong learning scale total score was 56.41±17.12. Students' lifelong learning tendencies differed significantly according to gender and grade. Male students' lifelong learning tendencies were higher than female students. Students' lack of learning and lack of curiosity mean scores differed significantly according to gender. The mean scores of the third and fourth grade students regarding lifelong learning, deprivation in regulating learning and lack of curiosity were significantly higher than the first and second grade students (18).

In another study, the lifelong learning tendencies of the students were very good. It has been found that there are differences in lifelong learning tendencies according to gender. Female nursing students' lifelong learning tendencies were higher than males. Deprivation in regulating learning and lack of curiosity subdimensions were significantly differed according to grade. Total YBÖÖ scores of female students had a higher rank average than males (19).

In a study conducted with teacher candidates, the deprivation in organizing learning and curiosity, the lifelong learning tendencies of the students differed significantly according to gender. Female students' lifelong learning tendencies were higher than males. It has been determined that female students' level of lifelong learning tendencies in deprivation in organizing learning and curiosity sub-dimensions was lower than males (20). In a study, curiosity scores of females were significantly higher than males (21). In another study, female students have a higher level of curiosity towards learning than males (22). Coşkun and Demirel (9), Kılavuz and Aydın (23), Kılıç (24), Karaduman and Tarhan (25), Çetin and Çetin (26) found that lifelong learning tendencies of female students were higher than males. On the other hand, Dikmen et al. (18), Dikmen et al. (27), Ekşioğlu et al. (28) found that lifelong learning tendencies of male students were higher than females. In another study, male students' lifelong learning tendency scores were significantly higher than females (29). In a study, it was observed that female students in each sub-dimension of lifelong learning were at a higher level than male students (8). In another study, students' lifelong learning tendencies were high, there was a significant difference in all sub-dimensions except the motivation sub-dimension. Lifelong learning tendencies of female students were higher than males (30). In studies, female students' lifelong learning were higher than males (13, 31). These differences that emerge in comparisons of lifelong learning tendencies according to gender is thought to be due to the difference in research method and samples.

In our study, it was found that the average of deprivation in regulating learning and the total score averages of lifelong learning tendencies differed significantly ($p<0.05$). Fifth grade students' average deprivation in regulating learning was significantly higher than the first grade students. The average deprivation in regulating learning of fifth grade students is significantly higher than the second grade students. It was determined that fifth grade students' deprivation in regulating learning average was significantly higher than the third grade. Fourth grade students' lifelong learning tendencies total score was significantly higher than the first grade students. Fifth grade students' lifelong learning tendencies total score was significantly higher than the first grade students. Similar to our study's results, in a study, first grade students' lifelong learning tendencies were lower than other grades. Second year students' scores in motivation subdimension were higher than fourth graders; first, second and third year students' scores on persistence dimension were higher than fourth grades. In the deprivation in regulating learning subdimension, the scores of the second and fourth grade students were higher than the first grade students and the fourth grade students were higher than the third grade. In the scores obtained from the deprivation in curiosity subdimension and the total of the scale, it was determined that the averages of the second, third and fourth grade students were higher than the first grade (4). In another study, there was no difference between medical school and nursing students in terms of lifelong learning and gender. Lifelong learning orientation of medical

students didn't differed according to grade (32). In a study, results indicated that the orientation toward lifelong learning tended to increase gradually along the education (33).

In our study, first grade students'lifelong learning tendencies scores were lower than other grades. In the literature, it is stated that lifelong learning takes place in different ways in every age period. In this context, one of the reasons why first grade students' lifelong learning tendencies are lower than other grades may be factors affecting lifelong learning tendencies such as "having more experience and learning habits" (34). In another study, the average of first grade students 'lifelong learning tendencies was lower than fourth grade students (9). In the study conducted by Atacanlı (35), the lifelong learning preferences of medical faculty students didn't differed significantly according to grade. In another study, lifelong learning tendencies of university students didn't differ according to their grade level (29).

In a study which examined the lifelong learning competencies of vocational high school students studying in different departments and classes Karakuş (36) found a significant difference between 1st and 2nd grade students. Level of the 2nd grade students' lifelong learning competencies was higher than the 1st grade (36). In another study, 1st grade students were at a higher level in each sub-dimension of lifelong learning tendencies than the 2nd and 3rd grade students (8). In a study, 3rd grade students' lifelong learning scores were lower than the other three grades (12).

In a study, it was observed that they had the highest average score in the motivation sub-dimension and the lowest average score in the lack of curiosity sub-dimension (15). In another study, students' motivation sub-dimension scores were high. In a study, students have a lifelong learning motivation, but their tendency to adapt this situation to different situations and to maintain their curiosity is lower than the motivation and persistence sub-dimensions. In the study, students' scores were lower in the deprivation in regulating learning and curiosity subdimensions (16).

In another study, it was found that students' lifelong learning tendencies are high (37). In a study, students' lifelong learning tendencies were at a medium level (38). As a result of the study of Karaman and Aydoğmuş (22), it was observed that the participants were at a very good level in motivation and persistence. In a study conducted with Turkish teacher candidates studying at the Faculty of Education program, it was observed that students in all subdimensions generally had a high average in the Lifelong Learning Scale (8). In a study conducted with nursing students, students' lifelong learning levels were low. They got the highest score from the "Curiosity Loss" subdimension and the lowest score from the "Motivation" subdimension (23). In the research conducted by Tunca et al. (4) on teacher candidates, the highest mean score was in the "Curiosity Deprivation" dimension and the lowest mean score was in the "Motivation" sub-dimension. In another study students' "Lack of Curiosity" subdimension mean score was highest. The lowest average score was in the "Motivation" subdimension (9).

On the other hand, there are studies in the literature in which lifelong learning tendencies were low. These studies were conducted among pre-service teachers, teacher candidates taking pedagogical formation and university students (4, 9, 28). As a result of another study, the average scores of medical faculty students ($X = 85.20 \pm 9.87$) were relatively lower than students from other faculties (39). In another study, clinical students scored significantly higher toward lifelong learning (40).

An important reason for these differences may be the differentiation of measurement tools used in studies, as well as the focus on different components of lifelong learning. The reason why the results differ in this way can be shown that the socio-demographic characteristics of the students and the departments they study in are different. It is observed that the main reasons for these differences are the differences between the study groups. In addition, it is thought that the differences in the content of lifelong learning in education curricula are also an important factor. Yet another reason may be the differences in the subtitles included in the scales. Another reason is that the professions and branches are different.

CONCLUSION

In line with the results obtained in the research, importance can be given to the development of lifelong learning tendencies in line with the activities to be carried out in the medical education program. Qualitative research can be conducted to investigate the reasons for the results of the research. In the light of the research findings, it can be said that there is a need to organize teaching-learning processes in medical faculties in order to gain lifelong learning competence. Suitable environments that support lifelong learning opportunities should be prepared and in this direction, on-campus and off-campus systems where students can easily access learning resources (library, internet, e-learning applications, courses, seminars, etc.) should be developed. Students should take orientation training for the use of information sources. In future studies, qualitative research can be conducted in addition to quantitative research on other factors that may be associated with lifelong learning tendencies.

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RESEARCH ARTICLE

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Analysis of the Efficiency and Cost of a Care Bundle for Prevention of Common Infections in an Intensive Care Unit: A Quasi-Experimental Pretest-Posttest Design Study

ABSTRACT

Objective: Healthcare-associated infections, threaten patient safety, cause prolonged hospitalization, morbidity, mortality and increased costs. This study was conducted to evaluate the effectiveness of interventions to prevent healthcare-associated infections and the effect of these interventions on cost.

Methods: A quasi-experimental pretest-posttest design study was completed between 1 January and 30 June 2018, and 1 October 2018 and 31 March 2019, in an intensive care unit, with a total of 54 patients, 27 pre-training and 27 post-training.

Results: In the study, infection rates were 20.34 in January to March 2018, 25.7 in April to June 2018, 20.97 in October to December 2018 and 17.77 in January to March 2019. When the infection rates of the four different periods were compared, it was found that there was a decrease compared to the pre-training period but that this decrease was not statistically significant ($p>0.05$). The average cost before the training was 11361.35₺ and the average cost after the training was 9149.87₺. Average bed costs, which are the most important of all costs, decreased by 25.7% compared to pre-training at the 95% confidence interval (5241.86₺-13251.50₺ and 3489.03₺-10257.41₺, respectively).

Conclusions: In conclusion, the study determined that training provided a significant increase in the intensive care nurses' scores related to healthcare-associated infections and there were decreases in healthcare-associated infection rates, lengths of hospital stay and cost after the training although these were not statistically significant.

Keywords: Healthcare-Associated Infections, Care Bundle, Nursing, Cost.

Bir Yoğun Bakım Ünitesinde Sık Görülen Enfeksiyonların Önlenmesi İçin Bir Bakım Paketinin Etkinlik Ve Maliyetinin Analizi: Yarı Deneysel Bir Öntest-Sontest Tasarım Çalışması

ÖZET

Amaç: Sağlık hizmeti ilişkili enfeksiyonlar hasta güvenliğini tehdit etmekte, hastanede yatış süresinin uzamasına, morbidite, mortalite ve maliyetlerin artmasına neden olmaktadır. Bu çalışma, sağlık hizmeti ilişkili enfeksiyonları önlemeye yönelik müdahalelerin etkinliğini ve bu müdahalelerin maliyete etkisini değerlendirmek amacıyla yapılmıştır.

Gereç ve Yöntem: Bu araştırma bir yoğun bakım ünitesinde 1 Ocak – 30 Haziran 2018 ile 1 Ekim 2018 – 31 Mart 2019 tarihleri arasında 27 eğitim öncesi ve 27 eğitim sonrası olmak üzere toplam 54 hasta ile yarı deneysel ön test-son test tasarım çalışması olarak yapılmıştır.

Bulgular: Çalışmada enfeksiyon oranları Ocak-Mart 2018'de 20.34, Nisan-Haziran 2018'de 25.7, Ekim-Aralık 2018'de 20.97 ve Ocak-Mart 2019'da 17.77 olarak bulunmuştur. Dört farklı dönemin enfeksiyon oranları karşılaştırıldığında, eğitim öncesine göre eğitim sonrasında enfeksiyon oranlarında azalma olduğu ancak bu düşüşün istatistiksel olarak anlamlı olmadığı saptanmıştır ($p>0.05$). Eğitim öncesi ortalama maliyet 11361.35₺, eğitim sonrası ortalama maliyet 9149.87₺ olarak belirlenmiştir. Tüm maliyetlerin en önemlisi olan ortalama yatak maliyeti eğitim öncesine göre %95 güven aralığında %25,7 oranında azalmıştır. (5241.86₺-13251.50₺, sırasıyla 3489.03₺-10257.41₺).

Sonuç: Sonuç olarak, çalışmada eğitimin yoğun bakım hemşirelerinin sağlık hizmeti ilişkili enfeksiyonlara ilişkin puanlarında anlamlı bir artış sağladığı, sağlık hizmeti ilişkili enfeksiyon oranlarında, hastanede kalış sürelerinde ve eğitim sonrası maliyette istatistiksel olarak anlamlı olmasa da azalma sağladığı belirlenmiştir.

Anahtar Kelimeler: Sağlık Hizmeti İlişkili Enfeksiyonlar, Bakım Paketi, Hemşirelik, Maliyet.

INTRODUCTION

Healthcare-associated infections (HCAIs), which are an important health problem, are accepted as the most important indicators of the quality of care in hospitals. The most common HCAIs in the intensive care unit (ICU) are catheter-associated urinary tract infection (CA-UTI), ventilator-associated pneumonia (VAP) and catheter-associated bloodstream infection (CA-BSI) (1). Healthcare infections increase morbidity, mortality, long-term disability, hospital stay, microbial resistance to antibiotics, and healthcare costs (2,3).

HCAI prevention and control is very complex and multidimensional approaches and strategies such as hand hygiene, surveillance, cohort studies and patient safety are required to address this important issue (4). Patient safety is an important topic, and this includes infection control. By integrating infection control programs with quality improvement programs in hospitals, HCAI rates can be monitored and the attempt can be made to prevent in-hospital spread (5). Studies on the prevention of the HCAIs show that it is possible to achieve the goal of zero nosocomial infections with the implementation of a bundle of proven interventions to prevent a specific nosocomial infection (6,7). According to the evidence from these studies, it is necessary to integrate care bundles for intensive care patients. In cases where compliance is kept at a high level, in particular, the effectiveness of care bundles increases and causes a significant decrease in mortality and morbidity (7-10).

HCAI's have considerable economic impact on health care services and the cost of national health care. Infections require increased treatment costs (for example drug therapy and procedures), involve increasing numbers of laboratory and diagnostic investigations and delay patient discharge. So investment in infection prevention and control is therefore highly cost-effective (10). Studies have shown that with the use of care bundles prepared based on the parameters in the guidelines, HCAIs decrease or can even be prevented (3,11-13). In this case, the prevention or even elimination of HCAIs means a decrease in costs. In a study investigating the cost effect of the hand hygiene compliance program in the ICU, it was concluded that the cost increased 2.5 times in patients with HCAIs compared to those without (14). In another study, in which a hospital cleaning bundle was applied to reduce HCAIs, it was determined that the application of a cleaning bundle provided cost savings of Australian dollars 147 500 (15). From this point of view, this study aimed to determine the effect of using care bundles in the prevention of HCAIs on infection rates as well as determining the effect on costs. In Turkey, this study is the first to study three important issues and costs of HCAIs. In addition, it will also contribute to the literature on the prevention of HCAIs.

MATERIAL AND METHODS

Study Design: The research was a quasi-experimental pretest-posttest study conducted to evaluate the effectiveness of interventions to prevent HCAIs and the effect of these interventions on cost.

Study Setting: The study was conducted at a state university hospital in Turkey in four stages: between 1 January and 30 June 2018; 1 October 2018 and 31 March 2019 (the study was interrupted for three months between 1 July 2018 and 30 September 2018 because it coincided with the annual leave period of the nurses). The research was conducted in the chest diseases ICU of the hospital. The chest unit provides services with a seven-bed capacity and a total of 14 nurses, two assistant doctors and two faculty members. The patient-nurse ratio is 2-3:1.

Universe and Sample: The population of the study consisted of patients hospitalized in the ICU between 2018 and 2019. The sample consisted of all patients hospitalized in the ICU between 1 January and 30 June 2018, and from 1 October 2018 to 31 March 2019.

The sample of the study was as follows: for VAP, all patients connected to mechanical ventilation; for catheter-related bloodstream infection, patients transferred to the ICU with a central catheter and a negative blood culture or a central catheter inserted by the intensive care doctor; for CA-UTI, all patients who were transferred to the ICU with a urinary catheter and had a negative urine culture or had a urinary catheter inserted in the ICU.

In addition, all patients with or without a catheter who were infected in the ICU were included in the study because of the possibility of developing a secondary infection. The study was completed with a total of 54 patients, 27 before the training and 27 after the training.

Data Collection: An Intensive Care Patient Data Form, a Socio-demographic Characteristics Form for Nurses, a Cost Analysis Table, the Pre-post Test Questionnaire for Nurses, and the Healthcare-Related Infections Prevention Care Bundle and Infection Prevention Care Bundle Control Form, developed by the researchers in consultation with the literature, wereused to collect the data.

The Intensive Care Patient Data Form featured 12 questions regarding the introductory characteristics of the patients, including age, gender, chronic diseases, glasgow coma scale, Apache II Score, the reason for hospitalization, intubation, presence of catheterization, antibiotic and steroid use, diet, and how patients left the ICU.

The Socio-demographic Characteristics Form for Nurses had six questions about the age, gender, education level, total time employed, time employed in the ICU, and previous training on HCAIs.

The Pre-postTest Questionnaire for Nurses was developed by the researcher after reviewing the literature in order to measure the knowledge of nurses working in the ICU about what points to

consider in terms of preventing the development of infection (13,16-22).

The Cost Analysis Table consisted of data obtained from patient invoices to determine the medical costs of the patient in line with Social Security Institution (SSI) indicators. While these data were requested from the accrual department of the institution, the amounts invoiced to the SSI for each patient were requested through the Cost Table Form. The cost data to be used in the calculation of the medical costs in the form of the cost table were collected in nine groups: service (injection, vascular access, blood collection), medicine, laboratory, examination, pathology, consumables, medical imaging, bed and complication expenses.

The Healthcare-associated Infections Prevention Care Bundle was prepared based on the prevention guidelines and the parameters in the guidelines issued by the Association for Hospital Infections and Control in Turkey infection (13,16-22)

The Infection Prevention Care Bundle Control Form was prepared to indicate the patient's first name and surname, file number, age, gender, diagnosis, and at what time each day of the month compliance was observed for each of the parameters in the Infection Prevention Care Bundle. The Infection Prevention Care Bundle Control Form was filled out by the first researcher and the nurse in charge of the ICU.

Study Procedure: The research was completed in four stages between 1 January - 30 June 2018, and between 01 October 2018 - 31 March 2019 (363 days).

Stage One: After obtaining the permission of the ethics committee and the institution, how the research would work was discussed with the responsible physician and nurse of the chest diseases ICU, and it was requested that the whole team (physician, other assistant personnel, etc.) be aware of this.

Stage Two: The second stage of the study covered the training of the ICU nurses with regard to HCAIs. The content was prepared by the researcher after examining the relevant literature (16-24).

The training was given to the nurses by the first researcher. The nurses were split into two separate groups and each session lasted approximately three hours, with interactive discussions accompanied by visual materials. Before starting the training, nurses were informed about the research, and their written consent was obtained. A pre-test was applied before the training and the same questions were asked again after the training was over. At the end of the training, information was given about how to use the Healthcare-Associated Infections Prevention Care Bundle. The nurses were told that they would apply this bundle four times a day (at 10:00, 16:00, 22:00, and 04:00 hrs) to the patients who met the inclusion criteria. The nurses were asked to go to the patients who met the criteria at the desired hours and check the parameters in the care bundle.

Stage Three: The third phase of the study started with the implementation of the care bundle after the training. The Intensive Care Patient Data Form and the Infection Prevention Care Bundle Control Form were filled in by the first researcher and the nurse in charge for all patients hospitalized in the ICU.

Stage Four: In the last stage of the study, the quarterly infection rates between 1 October 2018 and 31 March 2019 were examinedand overall compliance with the bundle was evaluated. Pre-training Cost Analysis Table outputs and post-training Cost Analysis Table outputs were compared.

Ethical Considerations: Approval was obtained from the Clinical Research Ethics Committee of a Training and Research Hospital in Turkey (Date: 2017, Number: 36) for the ethical viability of the study. Following this, permission was obtained from the institution where the study was conducted. Written consent was also obtained from the nurses.

Statistical Analysis: The data obtained in the research were analyzed using the IBM SPSS Statistics 22.0 package program. Descriptive statistics (number, percentage, mean, standard deviation, minimum, maximum), the Wilcoxon test, the Pearson chi-square test, t-test for dependent groups, t-test for independent groups, and the Kruskal-Wallis test were used in the analysis of the data. The statistical significance level was accepted as $p<0.05$.

RESULTS

It is seen that the mean age of the 14 nurses participating in the study was 29.21±4.82. 78.6% were female, 92.9% had a bachelor's degree, and they had been working in the ICU for an average of 5 years, and 78.6% of them have previously received training in HCAIs (Table 1).

Table 1. Demographical data of the nurses

Variable	Group	N	%
Age		29.21±4.82*	
Gender	Female	11	78.6
	Male	3	21.4
Nursing program completed last	Bachelor's degree	13	92.9
	Health vocational high school	1	7.1
Years of work in nursing		6.0±5.0*	
Years of work in intensive care		5.3±5.4*	
Healthcare-associated infections Training	Yes	11	78.6
	No	3	21.4

n: Number, %: per cent, *Average ± Standard Deviation

The nurses' mean scoresfor the nurses' pre- and post-education general HCAI test were 22.57±3.54 and 37.29±2.16 out of 40 points, respectively. It was observed that there was a significant increase in the scores of the nurses after the training (Z= -3.306, p=0.001). (Table 2).

Table 2. Pre-test post-test knowledge score distribution of nurses

	Pre-test		**Post-test**		**Test Statistics**
	x̄±SS	**Min-Max**	**x̄±SS**	**Min-Max**	
Healthcare-associated infections General Score	22.57±3.54	18-28	37.29±2.16	34-40	Z= -3.306, p=0.001*
Ventilator Associated Pneumonia Score	12.00±1.75	10-16	18.43±1.78	14-20	Z= -3.318, p=0.001*
Catheter Associated Bloodstream Infections Score	15.86±1.99	12-18	19.43±1.22	16-20	Z= -3.345, p=0.001*
Catheter Associated Urinary Tract Infections Score	12.29±1.89	10-16	18.71±1.49	16-20	Z= -3.330,p=0.001*
Total Score	62.71±6.00	52-72	93.86±4.25	86-100	t= -16.139, p<0.001**

Min: Minimum, Max: Maxium, *Wilcoxon Test, **T-test in dependent groups

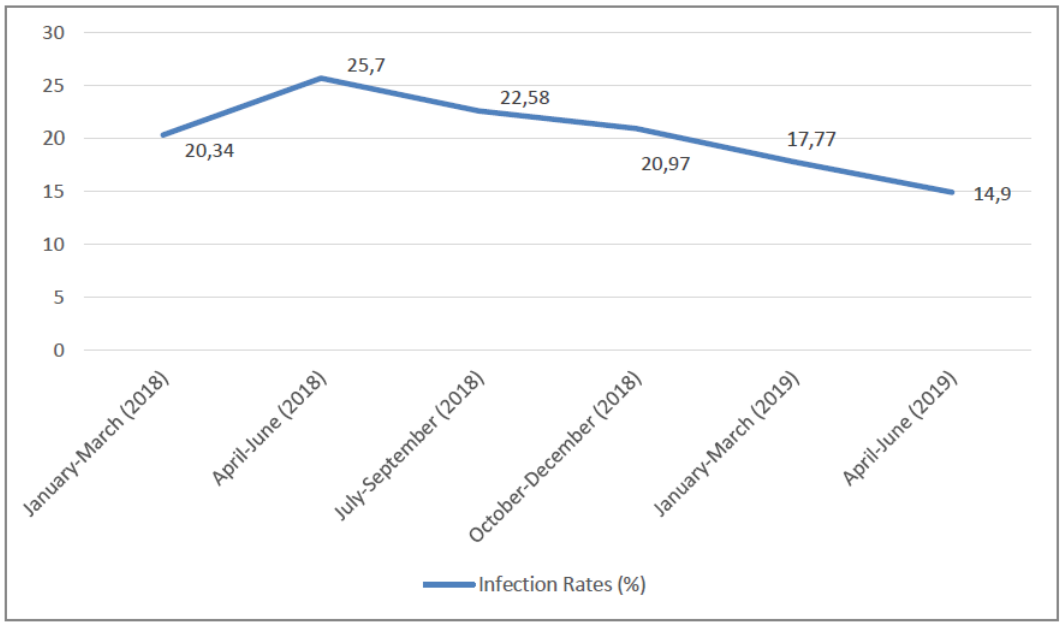
Although not given as a table, when we look at the compliance of the nurses to the Infection Prevention Care Bundle, it can be seen that compliance between 1 October and 31 December was 65%, while compliance between 1 January and 31 March was 63%.

Infection rates (in 1000 ventilation days) were 20.34 in the period January to March 2018, 25.7 in the period April to June 2018, 20.97 in the period October to December 2018, and 17.77 in the period January to March 2019. The infection rates of the four different periods were compared. As a result of the analysis, it was determined that the infection rates decreased compared to the pre-education period as seen in Chart 1 and it was determined that this decrease was not statistically significant (p>0.05) (Table 3; Graph 1).

Table 3. Comparison of the infection rates by periods

	January-March (2018)	**April-June (2018)**	**October-December (2018)**	**January-March (2019)**	**Test Statistics**
Number	12	14	13	11	χ2: 0.916*
Rate	20.34	25.7	20.97	17.77	p= 0.821

*Pearson chi square test



Graph 1. Infection rates by periods.

Although not given as a table, when the demographic data and disease characteristics of the patients before and after the education were examined, it was determined that all of them were similar and there was no statistical difference (p>0.05) between them.

The data on the costs obtained before and after the training in the study are presented in detail in Table 4. Accordingly, the average cost before the training was 11361.35₺ and the average cost after the training was 9149.87₺. The average cost of post-training decreased compared to pre-training. However, although this difference between the periods was not statistically significant (p>0.05), at the 95% confidence interval (6399.38₺-16323.32₺ and 4501.79₺-13797.95₺, respectively), the average cost was approximately 19% compared to the pre-training period. It is understood that this cost reduction was mainly because of the decrease in the infection rates and the decrease in the number of hospitalization days. In this context, average bed costs, which are the most important of all costs, decreased by 25.7% compared to pre-training at the 95% confidence interval (5241.86₺-13251.50₺ and 3489.03₺-10257.41₺, respectively). It was determined that there was no statistical difference in other sub-cost items (p>0.05) (Table 4).

Table4. Comparison of cost data by periods (₺)

Sort	Period	n	Min.	Max.	x̄	SS	SH	95% Confidence Interval		Test Statistics
								Lowest value	Upper value	
Beds	Pre-Training	27	584.00	38113.92	9246.68	10617.22	4004.82	**5241.86**	**13251.50**	p= 0.379* t= 0.887
	Post-Training	27	260.00	36524.85	6873.22	8971.84	3384.19	**3489.03**	**10257.41**	
Medicine	Pre-Training	27	0.00	10767.80	1466.77	2831.62	1068.08	398.69	2534.85	p= 0.770* t= -0.293
	Post Training	27	0.00	512.84	1741.39	3956.80	1492.50	248.89	3233.89	
Analysis	Pre-Training	27	0.00	527.88	223.07	119.96	45.23	177.84	268.30	p= 0.862* t= 0.174
	Post-Training	27	0.00	512.84	217.25	125.22	47.21	170.04	264.46	
Examination-Radiology	Pre-Training	27	0.00	33.68	10.64	9.21	3.46	7.18	14.10	p= 0.449* t= -0.768
	Post-Training	27	0.00	183.02	16.90	41.32	15.58	1.32	32.48	
Materials	Pre-Training	27	0.00	1192.79	212.28	241.16	90.96	121.32	303.24	p= 0.261* t= 1.137*
	Post Training	27	0.00	1100.62	141.16	217.89	82.18	58.98	223.34	
Consultation	Pre-Training	27	0.00	6.00	0.66	1.92	0.70	-.04	1.36	p= 0.180* t= -1.374
	Post-Training	27	0.00	36.00	2.66	7.31	2.74	-.08	5.40	
Blood Products	Pre-Training	27	0.00	584.90	68.77	151.01	56.95	11.82	125.72	p= 0.698* t= -0.390
	Post-Training	27	0.00	987.00	91.17	257.23	97.02	-5.85	188.19	
Intervention	Pre-Training	27	0.00	326.30	18.76	70.34	147.13	-128.37	165.89	p= 0.846* t= -0.195
	Post-Training	27	0.00	594.00	23.80	114.19	59.44	-35.64	83.24	
Other**	Pre-Training	27	0.00	1807.60	113.68	390.11	26.51	87.17	140.19	p= 0.382* t= 0.882
	Post-Training	27	0.00	799.20	42.27	157.64	43.06	-.79	85.33	
Total	Pre-Training	27	1008.05	45595.92	11361.35	13154.72	4961.97	6399.38	16323.32	p= 0.527* t= 0.638
	Post-Training	27	605.18	56145.37	9149.87	12322.56	4648.08	4501.79	13797.95	

n: Number, x̄: Average, Min: Minimum, Max: Maximum, SS: Standard Deviation, SH: Standart Error, *t-test in independent groups **İnvasive interventions

DISCUSSION

HCAIs are an important factor that increases costs due to the need for additional examinations and treatment interventions and prolongation of hospital stay (25). The economic dimension of HCAIs is a separate burden for the ICU due to both patient characteristics and treatment interventions (26). In the current study, it was concluded that the rate of infection, the length of hospital stay, and the associated cost decreased after the nurses' use of a care bundle developed for the prevention of common infections in the ICU. However, these decreases were not statistically significant. It is thought that the decrease in cost was due to the decrease in examination and treatment interventions due to the decrease in infection rates and the shortening of hospitalization.

When studies on the effect of the care bundle in the prevention of HCAIs are examined, parameters such as infection rate, length of hospital stay, and cost are discussed (3,27-30). In most of the studies, the evaluation criterion is infection rates, and studies examining the effect on cost are quite limited (31-33). In a study examining the effect of care bundle to prevent urinary catheter-related infections, it was concluded that a 71% reduction in infection rates was found with care bundle, and a cost savings of 30 816 $-120 696 $ per year (34).

In addition, Ferreira et al. (2016) found that the care bundle to prevent VAP provided a statistically significant reduction in hospital costs (35). Despite these studies in the literature, there are no cost-effectiveness studies in which the most common infections, CA-BSI, CA-UTI, and VAP are considered together in care bundle studies. Therefore, the results of this study will contribute to the literature in terms of both the use of care bundles for the three most common infections, and the cost analysis.

Studies on the prevention of HCAIs show that it is possible to achieve the goal of zero infections with the implementation of a care bundle of interventions with proven effectiveness to prevent a specific infection (3,11-13). In the current study, while the infection rates were 20.34/1000 ventilation days in the period January to March 2018, they were found to be 17.77/1000 in the period January to March 2019. It is seen that the infection rates indicate a decreasing curve compared to the previous year (Table 3; Chart 1). In addition, it was determined that the infection rates decreased when evaluated compared to the pre-education period, and this decrease was not statistically significant ($p>0.05$) (Graph 1).

HCAIs increase the length of hospital stay. In the study conducted by Jia et al. (2019), it was concluded that HCAIs cause an average increase of 10.4 days of hospitalization (36). In addition, the length of hospital stay is an important criterion used to evaluate the financial burden of HCAIs (37). In the study conducted by Leal and Freitas-Vilela (2021), it was concluded that the hospitalization cost of intensive care patients who developed HCAIs was four times higher than the patients who did not develop infections, and that there was a relationship between infection and longer hospital stay (38). In the study of Osme et al. (2021) with intensive care patients, it was stated that HCAIs prolong the length of stay in the hospital and place an extra burden on the health system (25). In the literature, examination of the economic dimension of HCAIs in the ICU is very limited, and existing studies have reached similar results to the present study (25,38). It is thought that the decrease in examination and treatment interventions in the present study, which was due to the decrease in infection rates and the shortening of the hospital stay, also caused a decrease in costs.

In the present study, as in the results of other studies, a significant increase was found in the knowledge scores of nurses about HCAIs (39,40). Although this was expected, the low level of compliance of nurses with the infection prevention bundle was not the desired result. In the literature, it is stated that the infection rate decreases when nurses' compliance with the infection prevention bundle increases (6,9,41,42). In the study conducted by Hassan and Wahsheh (2016) to determine the knowledge levels of intensive care nurses about VAP and its precautions, it was concluded that the knowledge levels of nurses increased significantly after the training (43). In a systematic review examining the effectiveness of education programs in VAP prevention, it was concluded that education provided a significant improvement in knowledge level and adherence to guidelines and a significant reduction in the incidence of VAP (44).

Although the knowledge of nurses increased in our study and the infection rates decreased following the application of the prevention bundle, the statistical insignificance of this decrease may be due to a decrease in compliance with the care bundle. From this point of view, it can be said that it is not enough to provide education on infection control alone, and strategies should be developed to increase compliance and behavioral change. Education can increase knowledge but may not lead to adaptations and changes to behavior.

There are limitations to the study, specifically that he sample was small. The limitation of the sample size could have been improved by prolonging the length of the study. In addition, a multicenter study could have yielded additional data.

CONCLUSION

In conclusion, this study determined that training provided a significant increase in the HCAI knowledge scores of the intensive care nurses, and there were decreases in HCAI rates, length of hospital stay, and cost after the training, although these were not statistically. The results of this study are similar to the literature in terms of showing the importance of infection prevention care bundles and it is thought that the study will aid future research by enabling the economic burden of HCAIs to be discussed using statistics. In addition, based on these results, it is recommended to conduct in-service training on care bundle in intensive care units and to repeat these trainings regularly.

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RESEARCH ARTICLE

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Interleukin-23R Gene Polymophisms in Patients with Diabetic Peripheral Polyneuropathy

ABSTRACT

Objective: Proinflammatory and neurovascular changes are blamed in the pathogenesis of diabetic neuropathy. Although it is accepted that diabetes is a trigger for vascular inflammation, it has been suggested that inflammation itself may trigger diabetes. Interleukin-23 (IL-23) is a pro-inflammatory cytokine secreted by activated macrophages and dendritic cells. Interleukin-23R is known to have a critical role in chronic inflammatory diseases. The aim of this study is to determine the relationship between IL-23R polymorphism and diabetic peripheral neuropathy.

Methods: 50 diabetic peripheral neuropathy patients who applied to Neurology outpatient clinic, and 52 healthy controls compatible with the patient group in terms of age and gender were included. Electromyography was performed on all of the volunteers, who agreed to participate in the study, and 2 ml of blood samples were taken into tubes with EDTA, and the IL-23R gene polymorphism was analyzed using the pyrosequencing method.

Results: IL-23R gene variants rs2201841, rs199542433, rs201052419, rs11209026 were analyzed in diabetic peripheral neuropathy (DPN) patients and control group. While we investigate IL23R polymorphisms we didn't find any significant differences between patient and control groups. But when we use odds ratios, rs2201841 seems to have a protective role, and rs199542433 in both dominant and recessive models and rs11209026 only recessive model seem to be related 10 fold higher risks for DPN.

Conclusions: IL-23R gene polymorphism has been shown to be associated with many autoimmune and inflammatory diseases. It is known that inflammation has an important effect on diabetes. The frequency of IL-23R gene polymorphism was not significant in diabetic peripheral neuropathy. Our study is the only and first study investigating the role of IL-23R gene polymorphism in diabetic peripheral neuropathy. Ethnicity is very important in genetic studies, and it will give us more clear information for the future to carry out this study in patients with other ethnic origins and to recruit larger study groups.

Keywords: Diabetic Peripheral Neuropathy, Inflammation, Genetics, Interleukin-23R (IL-23R) Gene Polymorphism.

Diyabetik Periferik Polinöropatili Hastalarda İnterlökin-23R Gen Polimofizmleri

ÖZET

Amaç: Diyabetik nöropatinin patogenezinde proinflamatuar ve nörovasküler değişiklikler suçlanmaktadır. Diyabetin vasküler inflamasyonu tetiklediği kabul edilse de inflamasyonun da diyabeti tetikleyebileceği öne sürülmüştür. İnterlökin-23 (IL-23) aktive makrofajlar ve dendritik hücreler tarafından salgılanan proinflamatuar bir sitokindir. Interleukin-23R'nin kronik inflamatuar hastalıklarda kritik bir rolü olduğu bilinmektedir. Bu çalışmanın amacı, IL-23R polimorfizmi ile diyabetik periferik nöropati arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Nöroloji polikliniğine başvuran 50 diyabetik periferik nöropati hastası ve hasta grubuna yaş ve cinsiyet açısından uyumlu 52 sağlıklı kontrol çalışmaya dahil edildi. Çalışmaya katılmayı kabul eden gönüllülerin tamamına elektromiyografi uygulandı ve EDTA'lı tüplere 2 ml kan örneği alındı. Pyrosequencing yöntemi ile IL-23R gen polimorfizmi analiz edildi.

Bulgular: IL-23R gen varyantları rs2201841, rs199542433, rs201052419, rs11209026 diyabetik periferik nöropati (DPN) hastalarında ve kontrol grubunda analiz edildi. IL23R polimorfizmleri sıklıkları açısından hasta ve kontrol grupları arasında anlamlı bir fark saptanmadı. Ancak, odd's oranlarına bakıldığında, rs2201841'in koruyucu rolü var gibi görünmekte, rs199542433 hem baskın hem de çekinik modellerde ve rs11209026 sadece çekinik modelde, DPN için 10 kata kadar daha yüksek risklerle ilişkili olabileceği görünmektedir.

Sonuç: IL-23R gen polimorfizminin birçok otoimmün ve inflamatuar hastalık ile ilişkili olduğu gösterilmiştir. İnflamasyonun diyabet üzerinde önemli bir etkisi olduğu bilinmektedir. Diyabetik periferik nöropatide IL-23R gen polimorfizminin sıklığı anlamlı değildi. Çalışmamız diyabetik periferik nöropatide IL-23R gen polimorfizminin rolünü araştıran tek ve ilk çalışmadır. Etnik köken, genetik çalışmalarda çok önemlidir ve bu çalışmanın başka etnik kökene sahip hastalarda yapılması ve daha geniş çalışma gruplarının alınması, bize ilerisi için daha net bilgiler verecektir.

Anahtar Kelimeler: Diyabetik Periferik Nöropati, İnflamasyon, Genetik, İnterlökin-23R (IL-23R) Gen Polimorfizmi.

INTRODUCTION

Diabetes Mellitus (DM) is an increasingly common disease. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (1). Complications could begin in the first years following the diagnosis of DM, or patients can be affected by complications at the time of diagnosis. Hyperglycemia, obesity, dyslipidemia, endothelial and intima changes, hyperinsulinemia, insulin resistance and genetic factors play a role in the development of chronic complications of DM (2,3).

Nerve damage in diabetic peripheral neuropathy (DPN) occurs as a result of metabolic factors, ischemia, and neurovascular changes. Inflammation and oxidative stress are veritably important in its etiology (4).

Subunits of interleukin (IL)-23 are IL-12 p40 and IL-23 p19. The IL-23R gene located on chromosome 1p31 encodes the IL-23 receptor. IL23R does not interact with IL-12, but pairs with IL12RB1 to confer IL23 responsiveness on cells expressing both subunits. It's secreted by macrophages and dendritic cells and can affect T-cell mediated inflammation and autoimmunity by impacting the response of T helper 17 (Th17) cells (5). The capability of IL-23R knockout mice to mediate inflammation is severely reduced (6). Langrish demonstrated the role of IL-23 in Th-17 development and its importance in inflammatory diseases (7). In a mouse model, IL-23 administration has been shown to have a destructive effect on pancreatic β-cells that cause hyperglycemia, suggesting that it may be effective in the development of autoimmune DM (8). Abbasi et al. found upregulation of the IL-23 gene in unstimulated mononuclear cells in type 1 DM patients (9). However, there is also a study concluded IL-23 serum concentrations did not differ significantly between diabetic patients and controls (10). It has been shown that variants of IL-23 Alpha (IL23A), a subunit of IL-23, are protective against type 1 DM, while IL-23R variants are not associated with DM (11). In vivo administration of IL-23 triggers late-onset diabetes in mice administered multiple low-dose streptozocin below the dose that can induce DM. This effect of IL-23 was associated with the expression of IL-17 and increased expression of Tumor Necrosis Factor-alpha (TNF-α) and IL-18 immediately after DM triggering (12).

DPN is a common and important microvascular complication of DM, affects roughly one-third of patients and impairs quality of life. It can affect small and large peripheral nerve fibers particularly in the lower extremities. Cytokines play an important role in DPN. Nerve conduction study in the diagnosis of DPN is important in terms of showing whether nerve involvement is axonal damage and/or demyelination (13). Various factors such as diabetes duration, HbA1c level, smoking and gender are effective in the development and frequence of DPN. Polyneuropathies are the most common group of DPN and can cause nontraumatic limb amputations (14). Cytokines have shown to be genetic markers in the development of microvascular complications of DM, such as DPN (15).

In our study, the role of IL-23R gene polymorphism in DPN was investigated as first study on this subject.

MATERIAL AND METHODS

After obtaining the Ethics Committee approval, 54 DPN patients who applied to neurology outpatient clinic between 2020-2021 and 53 healthy controls compatible with the patient group in terms of age and gender were included.

Type 2 DM patients aged 50-90 years with electroneurophysiologically detected DPN were included in the study. Those under the age of 50 and over the age of 90, those with inflammatory diseases such as Behçet's disease, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, ankylosing spondylitis, inflammatory bowel disease were not included in the study.

DPN was diagnosed according to Nerve conduction studies (NCS) recordings. All NCS measurements were performed with a Nihon-Kohden device (NihonKohden-Neuropack®) on three extremities of each subject including motor components of the peroneal, posterior tibial, median and ulnar nerves and sensory components of the sural, median and ulnar nerves. Nerve conduction velocities, distal latencies and amplitudes were recorded and interpreted by an experienced neurologist. Demyelinating neuropathy was diagnosed when prolonged distal motor latency, slowed conduction velocity, conduction blocks, and prolonged or absent F-wave latency while axonal neuropathy was diagnosed when low or loss of motor and sensory action potential was detected.

2 ml blood samples were taken from participants into EDTA tubes. DNA isolated with MiniBlood kit (Qiagen). After the isolation process was completed, 5 µL of DNA was distributed on the Polymerase Chain Reaction (PCR), for a total of 2 hours and 10 minutes, denaturation, bonding and elongation stages were performed as 95°C for 15 minutes, 94°C for 30 seconds, 60°C for 30 seconds, 72°C for 30 seconds, and 72°C for 10 minutes. Pyrosequencing was performed on the QIAGEN PyroMark Q24 instrument (QIAGEN, Inc., Valencia, CA, USA) for genotyping.

Collected data were digitalized and corrected. Among the variants studied in the IL-23R gene, rs2201841, rs199542433, rs201052419, rs11209026 were analyzed. Four from the patient group and one from the control group were excluded from the study due to the inability to obtain analysis results, and the study was evaluated on 50 patients and 52 control groups. Allele frequencies were calculated and compared between patient and control groups using

Chi Square test. When the expected value was less than five, the Fisher's exact test result was reported. The results were determined as wild, heterozygous mutant, homozygous mutant models. Odd's ratios for models for studied variants were computed and reported with 95% confidence interval (CI) limits. Test constants and absolute p values are presented for all analyses and $p<0.05$ was accepted as the general significance limit.

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RESULTS

Among the studied variants in the IL-23R gene, rs2201841, rs199542433, rs201052419, rs11209026 were analyzed in 50 DPN patients and 52 healthy controls included in the study.

In the DPN group, rs2201841 variant had 18 AA, 26 AG, 2 GT and 4 GG genotypes, rs199542433 variant had 47 CC and 3 CT genotypes, rs201052419 variant had 50 TT genotype and rs11209026 variant had 38 CG and 12 CC genotypes (Table 1).

In the control group, rs2201841 variant had 15 AA, 28 AG and 9 GG genotypes, rs199542433 variant had 49 CC and 3 CT genotypes, rs201052419 variant had 52 TT genotype and rs11209026 variant had 46 CG and 6 CC genotypes (Table 1).

Table 1. Allele frequencies

	DPN	Control	
rs2201841			
AA	18	15	X^2=4.232
AG	26	28	p=0.237
GG	4	9	
GT	2	0	
rs199542433			
CC	47	49	X^2=0.002
CT	3	3	p=0.961
rs201052419			
TT	50	52	Not calculated
rs11209026			
CC	12	6	X^2=2.724
CG	38	46	p=0.123

Odds ratio values were calculated by creating a recessive model and a dominant model for the patients and control groups (Table 2). There was no statistically significant difference between the DPN group and the control group in terms of allele frequencies ($P>0.05$). There was no significant difference between the DPN group and the control group in terms of homozygous wild and homozygous mutant genotype distribution for any variant. ($P>0.05$).

Table 2. Model results of genotype distributions

		Odd's ratio [95% CI]	Significance
rs2201841	**recessive model**	0.4155 [0.1191 - 1.4487]	Z=1.378, P=0.1681
	dominant model	0.7207 [0.3134 - 1.6573]	Z=0.771, P=0.4408
rs199542433	**recessive model**	10.396 [0.0202 - 53.4010]	Z=0.019, P=0.9846
	dominant model	10.426 [0.2003 - 53.4264]	Z=0.050, P=0.9605
rs201052419	**recessive model**	Not calculated	Not calculated
	dominant model	Not calculated	Not calculated
rs11209026	**recessive model**	10.396 [0.0202 - 53.4010]	Z=0.019, P=0.9846
	dominant model	0.4130 [0.1417 - 1.2042]	Z=1.620, P=0.1053

We found no difference between the patient and control groups in the rs2201841, rs199542433, rs201052419 variants, which may be due to the rarity of this variant in the total world population and European populations. In the rs11209026 variants our patient and control groups has higher frequency then European population, this can be because of founder affect of our small city population (Table 3).

Table 3. Frequencies of investigated IL-23R polymorphisms. (gnomAD. Genomes version 311)

	Total world population	European population
rs2201841	0.285	0.304
rs199542433 (p.Leu372Phe)	0.000215	0.0
rs201052419	0.00645	0.00494
rs11209026	0.0422	0.0586

DISCUSSION

DPN may develop in 60-70% of diabetic cases. Although the mechanisms involved in the development of neuropathy remain unclear, multifactorial risk factors included genetic predisposition and environmental factors.

Although genetic variants effective in the development of DPN have been found, it has not been clarified whether these variants are effective in the progression of the disease or they are specific for DPN (16). Although more than 60 loci that pose a risk to DM have been found, studies to determine the genetic risk factors of DPN are insufficient (17).

The IL-23 receptor complex consists of IL-23R and IL-12Rβ1. The second subunit is generally common in IL-12 receptor complexes. IL23R consists of extracellular domain (signal sequence, N-terminal immunoglobin-like domain and 2 cytokine receptor domains), a single transmembrane domain and a cytoplasmic domain. IL-23R is expressed on activated denritic cells, microglia, T cells, eosinophils, macrophages as well as on non-hematopoietic cells such as kerationocytes. Regulated expression of IL-23R plays a key role in leukocyte subset differentiation and processing. Factors that increase IL23R mRNA expression are IL-6, IL-21, T cell activation, TGFß (Transforming Growth Factor Beta) and IL-23 itself (18).

Interleukin-23R has been shown to have a critical role in a number of chronic inflammatory diseases such as chronic inflammatory bowel disease, psoriasis, Chrohn's Disease and arthritis in both mouse and human trials (19,20). IL-23 signal axis (IL-23/IL-23R) is an important inflammatory pathway (21).

Many theories have been suggested in the pathogenesis of DPN (22). One of them is oxidative stress and related inflammation. There is an increase in the levels of inflammatory cytokines such as IL-1, CRP, tumor necrosis factor (TNF)-α and IL-6 in patients with DM. Inflammatory cytokines are produced by various cell types and released into the circulation. Cytokines have local, central and peripheral effects on many different tissues. There is an increase in inflammation in type 2 DM and it is effective in the formation of many complications of DM, including DPN (23-25). On the other hand, there is also a study concluded that IL-23 serum concentrations do not differ significantly in DM patients and controls (10).

Investigated IL-23R polymorphisms didn't have any significant differences between patient and control groups. However, looking at the calculated odds ratios, rs2201841 polymorphism seems to have a protective role for DPN, rs199542433 polymorphism in both dominant and recessive model and rs11209026 polymorphism in recessive model seem to be associated with up to 10 times higher risk.

The main limitation of the study is the relatively low number of patients and controls included in the study. The representativeness of the studied sample for all diabetes and related DPN patients is uncertain. The COVID-19 pandemic has limited the number of patients and controls included in this study. New studies with larger groups will ensure that results are confirmed within the limit of significance. The study was conducted in a single center, geographical distribution differences of the investigated polymorphisms should be considered in the generalization and clinical use of the results. On the other hand, clinical and neurophysiological evaluation of patients and controls by the same neurologist is a valuable aspect of this study.

Genetic studies conducted so far have focused on the risk of developing type 2 DM. Most studies have been conducted focused on retinal and renal vascular complications diabetes. Although known effect of genetic factors and the inflammation in DPN, absolute risk factors and genetic predisposition remains unclear. Genetics studies in DPN are limited and reproducibility is lacking in most. Therefore, the investigation of new and rare variants is still important. We can reveal why many patients with the same risk factors experience different complications of DM with different severity by increasing genetic studies.

This is the first study to examine the risk of developing IL-23R gene polymorphisms in DPN patients. Our results suggest that the rs199542433 and rs11209026 polymorphisms, in particular, may be useful in identifying individuals at risk for DPN. The follow-up of patients with these polymorphisms would be the goals of future research.

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RESEARCH ARTICLE

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Evaluation of Pediatric Patients with First Seizure

ABSTRACT

Objective: Pediatric seizure is a condition that occurs due to many different underlying causes and causes fear and anxiety in families. In our study, it was aimed to evaluate pediatric seizure cases who applied to our hospital.

Methods: Patients aged 0-18 years, who applied to the pediatric emergency department of our hospital between May 2018 and May 2020, were retrospectively analyzed. The patients were evaluated in terms of age, gender, seizure types, familial genetic predisposition, examination, treatment and follow-up. Seizures were divided into 2 groups as focal and generalized according to the International League Against Epilepsy (ILAE) 2017 classification. The treatment methods applied with cranial magnetic resonance imaging and electroencephalography recordings of the patients were evaluated.

Results: Of the 118 patients included in the study, 70 (59 %) were girls and 48 (41 %) were boys. The mean age was 60 (3-192) months. Family history was present in 18 (15 %) cases. 8 (7 %) of the seizures are partial and 110 (93 %) of them are generalized. Since seizure recurrence was observed within 24 hours in 5 of 36 patients who were evaluated as febrile seizures, they were evaluated as complicated febrile seizures and drug treatment was started. The other 31 patients were evaluated as simple febrile seizures. There was no biochemical abnormality in the seizure etiology in any of the cases. Cranial magnetic resonance imaging revealed polymicrogyria in 2 patients, hydrocephalus in 2 patients, brain tumor in 1 patient, and arteriovenous malformation in 1 patient.

Conclusions: In cases presenting with seizures, the underlying causes should be identified and their treatment should be arranged. Cases with recurrent seizures should also be followed closely.

Keywords: Child, First Seizure, Treatment.

Çocuk Acile İlk Nöbet ile Başvuran Olguların Değerlendirilmesi

ÖZET

Amaç: Pediatrik nöbet, altındaki birçok farklı nedene bağlı oluşan ve ailelerde korku ile endişeye yol açan bir durumdur. Çalışmamızda hastanemize başvuran pediatrik nöbet olgularının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Mayıs 2018 ile Mayıs 2020 tarihleri arasında hastanemiz çocuk aciline nöbet ile başvuran 0-18 yaş arası hastalar retrospektif olarak incelendi. Hastalar yaş, cinsiyet, nöbet tipleri, ailesel genetik yatkınlık, tetkik, tedavi ve takip açısından değerlendirildi. Nöbetler International League Against Epilepsy (ILAE) 2017 sınıflamasına göre fokal ve jenaralize olarak 2 gruba ayrıldı. Hastaların kranial manyetik rezonans görüntüleme ve elektroensefalografi kayıtları ile uygulanan tedavi yöntemleri değerlendirildi.

Bulgular: Çalışmaya dahil edilen 118 hastanın 70 'i (%59) kız, 48' i (%41) erkekti. Yaş ortalaması 60 (3-192) ay idi. Aile öyküsü 18 (% 15) olguda mevcuttu. Nöbetlerin 8' i (% 7) parsiyel, 110' u (% 93) jenaralize nöbetti. Febril nöbet olarak değerlendirilen 36 hastanın 5' inde 24 saat içerisinde nöbet tekrarı görüldüğü için komplike febril nöbet olarak değerlendirilip ilaç tedavisi başlandı. Diğer 31 hasta basit febril nöbet olarak değerlendirildi. Nöbet etiyolojisinde hiçbir olguda biyokimyasal anormallik yoktu. Kranial manyetik rezonans görüntülemede 2 hastada polimikrogri, 2 hastada hidrosefali, 1 hastada beyin tümörü ve 1 hastada da arteriovenoz malformasyon saptandı.

Sonuç: Nöbet ile başvuran olgularda altta yatan nedenler tespit edilerek tedavileri düzenlenmelidir. Tekrarlayan nöbetleri olan olguların da yakın takibe alınması gerekmektedir.

Anahtar Kelimeler: Çocuk, İlk Nöbet, Tedavi

INTRODUCTION

There are channels in the brain that provide inhibition and excitation. Seizure is defined as an abnormal electrical neuron discharge in the brain. The incidence of seizure varies between 0.5 % and 0.8 % in various studies (1). It is a condition that occurs due to many different reasons and causes fear and anxiety in families. Today, with the progress in the genetics department, it has been determined that most cases have genetic etiology. Any damage to the cerebral cortex can also lead to the development of seizures. Fever, hypocalcemia, hypoglycemia, trauma, infection, meningitis, encephalitis, intracranial hemorrhage, intracranial mass, cerebral dysplasia can trigger seizures (2).

Evaluation of the patient is important in predicting the cause of the seizure, the need for treatment with antiepileptic medication, the potential for response to treatment, and future recovery (3). Seizure-related morbidity and mortality require the implementation of seizure control strategies (4). Knowing the seizure types, frequency, general characteristics and resistant seizure rates of the patients admitted to the hospital will be of great benefit in patient management (5).

In this study, considering the diagnostic criteria of International League Against Epilepsy (ILAE) 2017 seizure types, causes of seizures, accompanying risk factors, recurrences, clinical course, medical and familial history of the patients, and electroencephalography It was aimed to evaluate (EEG) recordings, brain magnetic resonance imaging (MRI) findings and drug treatments applied.

MATERIAL AND METHODS

Pediatric cases under the age of 18 years, who were brought to the Pediatric Emergency Department of our hospital due to epileptic seizures between May 2018 and May 2020, were included in the study and the data were analyzed retrospectively. The patients included in the study were followed up, and the families were informed, and a consent form was obtained for the study. Ethical approval (ODU KAEK 17.09.2020/19/183) was obtained from Ordu University Clinical Research Ethics Committee for the study.

In the pediatric emergency, the first emergency interventions of the patients were performed first. Afterwards, the child was taken into observation and evaluated by neurology. Age, gender and familial genetic predispositions of the patients were questioned. Accompanying metabolic imbalance, fever were examined. Seizures were divided into 2 groups as focal and generalized according to the ILAE 2017 classification (6). The seizure that occurred 24 hours after the first seizure was considered as seizure recurrence. Conditions such as syncope, wheezing, tics, and movement disorders that were not considered as seizures after presenting with the complaint of seizures were not included in the study. Cases who did not have a first seizure and had seizure uncertainty in the past were not included in the study. The cases who had the first seizure when they applied to the emergency department and were followed up for one year were included in the study.

Cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) records of the patients who were followed up were evaluated. The antiepileptic drugs used, how long they were used, their doses, and whether they were used regularly were monitored throughout the study.

Statistically Analysis: The data were analyzed by SPSS 15.0 (SPSS Inc., Chicago, IL, USA) program. Shapiro-Wilk test was used to find out whether the data were distributed normally. The data which were normally distributed were expressed in terms of average±standard deviation, while the data which were not normally distributed were expressed in terms of mean (min-max).

RESULTS

Of the 118 patients included in the study, 70 (59 %) were girls and 48 (41 %) were boys. The mean age was 60 (3-192) months. Fifty (42.3 %) of the patients were under the age of 6, 36 (30.5 %) were between the ages of 6-12, and the remaining 32 (27.2 %) were between the ages of 12-18 (Table 1).

Table 1. Characteristics of patients

Age (year)	***n (%)***
< 6	50 (42.3 %)
6-12	30 (30.5 %)
>12	32 (27.2 %)
Gender	***n (%)***
Male	48 (41 %)
Female	70 (59 %)
Seizure type	***n (%)***
Parsial	8 (7 %)
Generalize	110 (93 %)
Total	**118**

Eight patients (7 %) of the seizures are partial and 110 (93 %) of them are generalized. Thirty-two of 36 patients, who were evaluated as seizures accompanied by fever, were under the age of 6 and were considered as febrile seizures. Since seizure recurrence was observed within 24 hours in 5 of 36 patients who were evaluated as febrile seizures, they were evaluated as complicated febrile seizures and drug treatment was started.

There was no biochemical abnormality in the seizure etiology in any of the cases. Cranial magnetic resonance imaging revealed polymicrogyria in 2 patients, hydrocephalus in 2 patients, brain tumor in 1 patient, and arteriovenous malformation in 1 patient (Table 2). Partial seizure were observed in brain tumor, arteriovenous malformation and 1 hydrocephalus patient.

Table 2. Magnetic rezonans imaging findings

Pathology	***n (%)***
Polymicrogyria	2
Hydrocephalus	2
Brain tumor	1
Arteriovenous malformation	**1**

Family history was present in 18 (15 %) cases, was found to be 11 in 36 patients with febrile seizures. Of these patients, 2 had complicated febrile seizures, 8 had simple febrile seizures, and 1 had seizures accompanied by fever over the age of 6 years. 4 of 50 patients under the age of 6 who had seizures were being followed up in child psychiatry because of special learning difficulties.

EEG was applied to all of the patients and abnormality observed in 42 of them. In cases with abnormality in brain MRI, localization finding was observed in EEG. EEG was normal in cases evaluated as simple febrile seizures. Medication was recommended to all patients with EEG abnormalities. Valproate and levetiracetam were started for generalized seizures, and carbamazepine or oxcarbamazepine was started for those with focal seizures. Phenobarbital was started in patients under 2 years of age who were prescribed medication. Seizure recurrence was observed in 18 of 42 patients with EEG abnormality, and drug doses were adjusted.

DISCUSSION

Seizure is defined as excessive and abnormal brain discharge in the brain (7). While various genetic, metabolic and neurological conditions may be involved in its etiology, no cause may be detected. Its incidence is stated as 1% (8). It has been observed that 75% of epilepsies in adulthood begin in childhood (9).

Hamiwka et al. male/female ratio has been reported as 0.7 in epilepsy cases (10). Berg and Shinnar reported an equal male/female ratio in their study (11). Okumura et al. reported the age range as 7-69 months in their studies and 1-77 months in the Ling study (12,13). In our study, the male/female ratio was 0.68, the age range was 3-192 months, and the mean age was 60 months.

Although genetic factors are known to play a role in the development of seizures, genetic transmission has not been fully elucidated (3). Family history of epilepsy has been reported as 7.5-9.7% in studies (1). In our study, a family history of epilepsy was found at a rate of 15%. 11 of these 18 cases were febrile seizures. A history of febrile seizures in first-degree relatives, having the first seizure under the age of one, presence of fever for a short time before the seizure, and low-grade fever during the first febrile seizure are listed as factors that increase the risk of recurrence of the febrile seizure (14).

EEG is frequently used in the diagnosis of seizures, classification of seizures, and the decision to start treatment (9). Having a sleep EEG and applying hyperventilation-photic stimulation in the EEG increase the frequency of pathology detection. Camfield et al. found anomaly in neurological findings, spike-wave finding in EEG and seizure recurrence rate of 96% in the presence of accompanying complex partial seizures (15). EEG was applied to all of the patients and abnormality observed in 42 of them. In cases with abnormality in brain MRI, localization finding was observed in EEG. EEG was normal in cases evaluated as simple febrile seizures. In the literature, the rate of abnormal findings in brain MRI has been reported as 14% (9). MRI was also performed in all cases included in our study. During the MRI, some children did not stop due to age, so chloralhydrate was given to the patients as a medicine and they were anesthetized. Cranial magnetic resonance imaging revealed polymicrogyria in 2 patients, hydrocephalus in 2 patients, brain tumor in 1 patient, and arteriovenous malformation in 1 patient. In our patients, the rate of MRI pathology was found to be 5%, which is lower than the literature. This situation has been associated with more febrile seizures coming to the pediatric emergency room.

In cases evaluated with seizures, drug treatment is decided according to seizure type, etiology, familial history, and whether there is an abnormality in EEG or MRI (16). There is a wide variety of antiepileptic treatments available (17). While antiepileptic is not recommended for simple febrile seizures, it is recommended in complicated febrile seizures. (18). Proper use of anti-epileptic therapy should be controlled with intermittent blood tests. Families should be informed about drug allergy. In our cases medication was recommended to all patients with EEG abnormalities. Valproate and levetiracetam were started for generalized seizures, and carbamazepine or oxcarbamazepine was started for those with focal seizures. Phenobarbital was started in patients under 2 years of age who were prescribed medication. Seizure recurrence was observed in 18 of 42 patients with EEG abnormality, and drug doses were adjusted.

Although simple febrile seizure should not be hospitalized if the patient is in a good condition, hospitalization for observation is necessary when a child presents with red flag sign and symptoms (4). We kept the all cases under surveillance at least 12 hours against complication.

The limitations of the study are that the data on seizure types were obtained from the descriptions of the families, and we had limited resources and information to determine the underlying causes of the first seizure as of the date of the study. The maximum observation period of the patients is 2 years, and the longer follow-up period in these diseases with long-term treatment will provide more reliable information.

In conclusion, it is important to correctly classify seizures in patients presenting with the first seizure, to investigate the etiology, to start medication in patients diagnosed with epilepsy, to follow up the patients in terms of drug side effects and clinically.

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RESEARCH ARTICLE

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Does Saccharin Have Effects on Appetite, Energy Intake, And Serum Ghrelin? A Randomized, Controlled, Cross-Over Study in Healthy Males

ABSTRACT

Objective: Instead of sugar, artificial sweeteners that do not contain energy are widely used. However, contrary to popular belief, artificial sweeteners are thought to affect metabolism. Thus, purpose of this present study was to evaluate effects of saccharin on serum ghrelin, appetite, and food consumption.

Methods: Nine healthy males aged 20-29 participated in the randomized, controlled, and cross-over study. Each participant received 300 ml water, and 300 ml water containing 75 grams sucrose and 240 milligrams saccharin. At baseline, 30th, 60th, 90th, 120th, and 180th min, Visual Analog Scale was applied to evaluate appetite, and blood samples were taken to analyze ghrelin. After 180th min, participants consumed ad libitum diet, and kept 24-hours dietary food intake records until the end of this day.

Results: At 60th and 120th min, mean ghrelin level was higher in drinks containing only water and saccharin compared to drink containing sucrose ($p=0.001$, $p=0.003$ respectively). In addition, in 90th min following drink consumption, mean ghrelin level was higher in drink containing saccharin than sucrose test drink ($p=0.001$). Mean prospective food consumption and desire to eat score at 120th min after drink consumption was higher in saccharin test drink than sucrose test drink ($p<0.05$). Difference between energy and macronutrient intake was statistically insignificant ($p>0.05$).

Conclusions: In this study, which examined the effect of acute intake of saccharin an artificial sweetener, it is remarkable that high ghrelin levels and high scores related to appetite in some intervals after drink consumption containing saccharin. However, studies on the longer-term consumption of saccharin are needed to clarify these effects on appetite metabolism.

Keywords: Saccharin, Energy Intake, Appetite, Ghrelin Level, Artificial Sweetener.

Sakarinin İştah, Enerji Alımı ve Serum Ghrelin Üzerinde Etkisi Var mı? Sağlıklı Erkeklerde Randomize, Kontrollü, Çapraz Bir Çalışma

ÖZET

Amaç: Günümüzde şeker yerine enerji içermeyen yapay tatlandırıcılar yaygın olarak kullanılmaktadır. Ancak bilinenin aksine yapay tatlandırıcıların metabolizmayı çeşitli yönlerden etkilediği düşünülmektedir. Bu çalışmanın amacı sakarinin serum ghrelin düzeyi, iştah ve besin tüketimi üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntem: Randomize, kontrollü ve çapraz olarak yapılan çalışmaya 20-29 yaşları arasında dokuz sağlıklı erkek katılmıştır. Her katılımcıya 300 ml su, 75 gram sükroz içeren 300 ml su ve 240 miligram sakarin içeren 300 ml su verilmiştir. Başlangıç, 30., 60., 90., 120. ve 180. dakikalarda iştahı değerlendirmek için Görsel Analog Skala uygulanmış ve ghrelin analizi için kan örnekleri alınmıştır. Yüzsekseninci dakikadan sonra katılımcılar ad libitum beslenmişler ve her uygulama gününün sonuna kadar 24 saatlik besin tüketim kaydı tutmuşlardır.

Bulgular: Altmışıncı ve 120. dakikalarda sadece su ve sakarinli içeceklerde ortalama ghrelin düzeyi sükroz içeren içeceğe kıyasla daha yüksektir (sırasıyla $p=0.001$, $p=0.003$). Ayrıca içecek tüketimini takip eden 90. dakikada sakarin içeren içecekte ortalama ghrelin düzeyi sükroz içerene göre daha yüksektir ($p=0.001$). İçecek tüketiminden sonraki 120. dakikada ortalama besin tüketme potansiyeli ve yemek yeme isteği skorları, sakarin test içeceğinden sonra sükroz test içeceğine kıyasla daha yüksektir ($p<0.05$). Enerji ve makro besin ögesi alımlarında uygulamalar arasında farklılık bulunmamıştır ($p>0.05$).

Sonuç: Bir yapay tatlandırıcı olan sakarinin akut tüketim sonuçlarının incelendiği bu çalışmada, sakarin uygulamasında bazı ölçüm zamanlarındaki ghrelin düzeyinin ve iştah ile ilgili skorların yüksek olması dikkat çekicidir. Ancak iştah metabolizması üzerindeki bu etkilerin netlik kazanması için, sakarinin daha uzun süreli tüketimini ele alan çalışmalara gereksinim vardır.

Anahtar Kelimeler: Sakarin, Enerji Alımı, İştah, Ghrelin Düzeyi, Yapay Tatlandırıcılar

INTRODUCTION

Artificial sweeteners are defined as food additives frequently used in different foods and drinks that give an intensely sweet taste and reduce the energy density of the foods and drinks (1). In the communique, which covers sweeteners used to sweeten food and drinks prepared by the Turkish Food Codex Regulation and sweeteners offered directly to the consumer (2). Although the safety of artificial sweeteners such as aspartame, acesulfame potassium, advantame, neotame, saccharin, stevia, and sucralose have been approved by the Food and Drug Administration of America (FDA) (3), the results of the studies on the health effects of sweeteners cause controversy (4-6). Because the studies show that sweeteners are localized in the small intestine, and their mechanisms are not only related to taste in the tongue (4).

In this study, saccharin, used as an artificial sweetener, is 300 times sweeter than sucrose and was approved by the FDA in 1970 (7, 8). It is resistant to heat and acidity, and the acceptable daily intake (ADI) level determined by the FDA is 5 mg/kg/day (9). Eighty milligrams (mg) saccharin can provide 25 g sucrose's sweetness in quantity (10). Saccharin, first discovered in 1878, has the oldest historical background compared to all of the artificial sweeteners used to present (11). Saccharin, the only artificial sweetener used in the United States for a while, was proposed to be banned by the FDA in 1977 in line with the results of animal studies. However, this caused reactions, and it was decided that more studies should be conducted, and a warning label should be mandatory on all products containing saccharin. Based on the results of subsequent studies, although the effects of saccharin on human metabolism could not be clearly explained, it was removed from the carcinogen list in 2000, and the requirement to have warning labels that showing saccharin ingredient in products was removed (12). Today, artificial sweeteners are used in many products such as soft drinks, diet drinks, diet desserts, chewing gums, candies, biscuits, and crackers (1).

Weight gain and other adverse health outcomes due to frequent consumption of sugar-sweetened foods and drinks increased the trend towards the consumption of artificial or non-nutritional sweetener-containing products. However, sweeteners are not physiologically inert compounds. Potential biological mechanisms of sweetener consumption that may affect energy balance, metabolic function, effects on hormone release, cognitive processes, intestinal microbiota, and taste receptors should be investigated (13).

People might easily consume artificial sweeteners and foods and beverages containing these sweeteners to limit their daily energy intake, thinking that they will not harm their health and that they will not exceed the acceptable daily intake. However, until recently, these sweeteners were thought to be metabolically ineffective in the human body, some recent studies have led to some doubts that it increases ghrelin secretion and appetite (6, 14-16). Although the effects of various these sweeteners have been investigated in the mentioned studies, preferring saccharine as an artificial sweetener, and giving the standard breakfast to the participants in this study expresses the novelties of the study. In addition, the most important is the first study conducted with healthy people in Türkiye focused on the food consumption effects of saccharin that frequently is used in packaged products, beverages and is sold in boxes alone. It was hypothesized that saccharin can affect the blood ghrelin level, increase energy intake by changing appetite so that saccharin can act like sugar in the body. Therefore, this study was conducted to evaluate the effects of sucrose and the non-energy sweetener saccharin on the ghrelin hormone, appetite, and energy intake in healthy adult males.

MATERIAL AND METHODS

Participants: Informative posters were placed on the boards of the Faculty of Health Sciences, Ankara University, and interested people were asked to come to the study room. It was decided that volunteers were accepted for the study after being evaluated to meet the inclusion criteria of the study. In the study, volunteer male was found that between the ages of 20-29, having normal body weight (body mass index 18.5-24.9 kg/m^2), not exercising regularly, not having weight change more than 3 kilograms (kg) in the last six months, not having any disease diagnosed by the physician, who do not have gastrointestinal problems and food allergy/intolerance, have not undergone any surgery in the last one year, not taking prescription medication, not having disease diagnosed by a physician, not using non-prescription drugs, supplementation or pre-probiotic, and did not consume foods containing sweeteners and/or sweeteners in the last one week were included.

Ethics: The study was conducted in accordance with the Declaration of Helsinki. The study protocol received institutional review board approval and that all participants provided informed consent in the format required by the relevant authorities and/or boards. All procedures were approved by the Ethics Committee of the University Clinical Research Ethics Committee of Ankara University (Decision No: 17-1171-19, dated 2019). The participants' principle of volunteering was taken as a basis, and each participant signed the informed volunteer consent form.

Research Design: '3*3 Latin Square Trial Design' was used in the research to calculate the number of participants. According to this study design, all trials were applied to each individual to eliminate individual differences. At the beginning of the experiment, it is necessary to apply all tests

to all individuals and do randomize for determination of which application to start with. Since there are three different applications in the study, it was found adequate to be done with nine volunteers according to the mentioned Latin square trial design (17). Also, some similar studies evaluating the effects of aspartame and sucralose on glucose homeostasis and appetite were included in the study were considered when calculating this number. There were ten and eight subjects respectively in these studies of Tey et al., and Brown et al. (5, 18). Since it is known that women's energy intake varies before, during and after the menstrual cycle, only men were included in the study (19). The inclusion of only males in the study ensured that interindividual differences were minimized and increased the reliability of the study data.

Before the participants were included in the study, basic anthropometric measurements (body weight, height) were taken to evaluate their body mass index (BMI). All anthropometric measurements were measured in accordance with the technique and method (20). Participants with body mass index <18.5->24.9 kg/m^2 were not included in the study. Body fat ratios, muscle mass, and visceral fat levels of those with normal body weight were determined with a personal body analyzer (TANITA BC601) while having an empty stomach, wearing thin clothing, and without shoes. It was taken into consideration that the participants had similar characteristics in terms of body composition. Then, the general and health information of the participants was questioned.

Participants who did not have regular exercise habits were asked to record 24-hour physical activity on any day of the week since their different physical activity levels may affect the study results, especially their appetite. The total energy expenditure was obtained by multiplying minutes of activity types with activity factors related to the type of activity being calculated. Then this total energy was divided by 1440 to find the physical activity level. Participants with a physical activity level of 1.40-1.69 were considered sedentary or slightly active, participants with 1.70-1.99 as active or moderately regarded as active, participants with 2.00-2.40 considered severely active. Only sedentary or slightly active participants were included in the study. It was ensured that the participants sit and wait during the study after fasting for at least 10 hours (h) and did not consume anything other than the experimental design samples. It was stated to the participants that they should not consume foods and beverages containing sweeteners at least one week before starting the study, avoid heavy physical activity before each application day, do not consume anything unusual at dinner, maintaining the usual diet, and come with at least 10 h of hunger on the day of the application. The consumption status of the participants before the interventions was confirmed by evaluating the Continuous Glucose Monitoring System (GCMS-Medtronic iPro) reports placed the day before. After making sure that they did not consume anything, their data were included in the study. The inclusion criteria and the flow diagram of the study are shown in Figure 1.

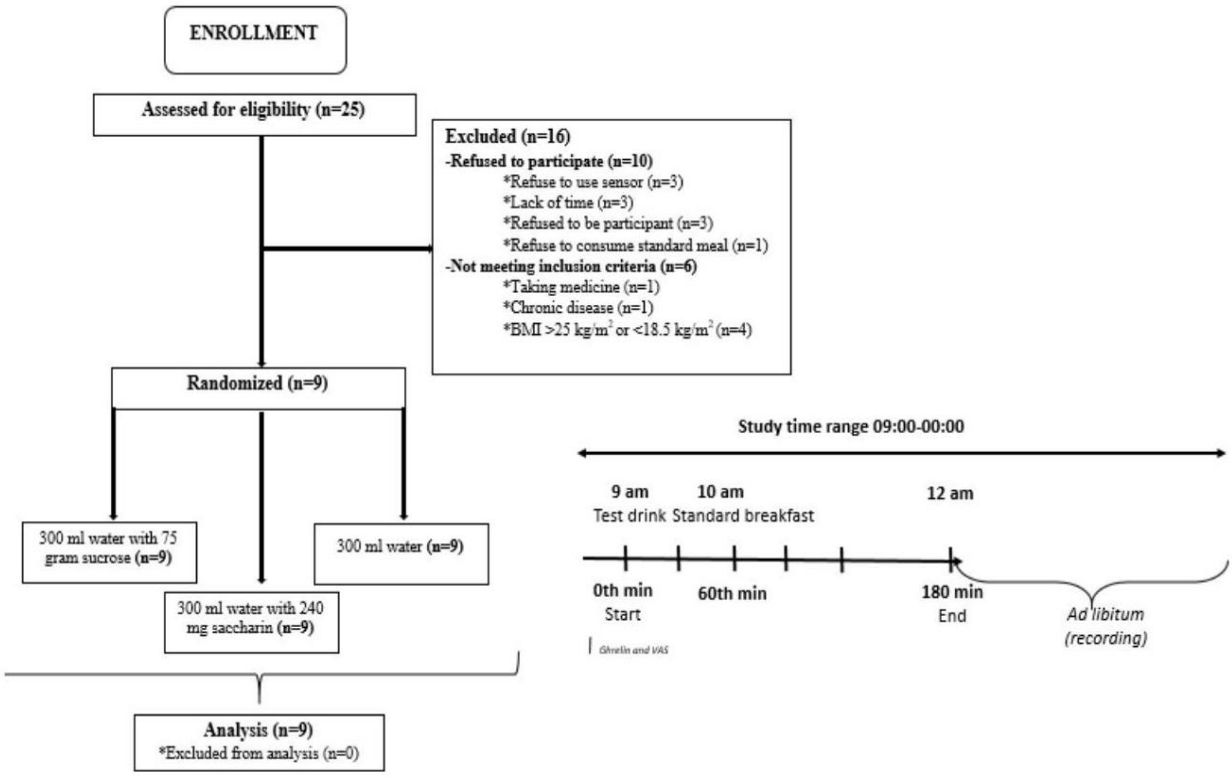

Figure 1. Flow diagram of study

Test Drinks and Breakfast Meal: This study was planned as a randomized and cross-over design. There was a washout time of 4-7 days between trials for each participant. The test drinks to be applied in the study were planned as 300 ml of water containing 75 grams (g) of sucrose (tea sugar), 300 ml of water containing 240 mg of saccharin with the same sweetness, and 300 ml of plain water without any sweetener added. Participants received 3.7±0.51 (2.8-4.3) mg saccharin per kg. It has been ensured that there were at least five days between the consumption of each test drink. Participants were asked to finish their test drinks within 5 minutes. Saccharin was chosen because it is one of the most used artificial sweeteners, especially in Türkiye.

A breakfast meal consisting of a standard 100 g white bread, 60 g white cheese, 150 g apple, and 200 ml unsweetened tea was planned 60 min after consuming the test drink. Breakfast contains 488 kilocalories (kcal) of energy, 80 g of carbohydrate, 20 g of protein, and 10 g of fat. By serving breakfast meals, complications related to prolonged hunger were prevented, and the effect of hunger on the data to be obtained was prevented. Participants were asked to finish breakfast within 20 min.

The individuals were asked to come to the Nutrition Principles Laboratory of the faculty at 08:50 on the application days, they were given a test drink at 09:00, and they were made to consume breakfast at 10:00. Blood samples were taken at 0., 30., 60., 90., 120. and 180. min to determine the serum total ghrelin level and to evaluate the effect of test drinks on the ghrelin level.

After obtaining the data, the participants were asked to return to their routine lives and to record in detail the food and drinks they consume as ad libitum until the end of the day (00:00). The daily energy and nutrient amounts of the participants from the food consumption record were calculated with the BEBİS 7.2 (Nutrition Information System) program.

Appetite Assessment: In order to evaluate the appetite of the participants, Visual Analogue Scale (VAS) was applied immediately after blood samples were taken at 0., 30., 60., 90., 120. and 180. min. With the Visual Analogue Scale (VAS), they were asked to evaluate their appetite between "not hungry at all" (0 mm) and "very hungry" (100 mm). The questions about appetite on the scale are hunger, satiety (fullness), prospective (forward-looking) eating power, estimated amount of food, and the estimated amount of sugary food consumption. The answers given by the participants to the VAS questions were quantitatively valued with the help of a 100 mm VAS scale.

Blood Analysis: Intravenous blood samples were taken for blood ghrelin analysis. An intravenous (intravascular) cannula was placed in the participants by the research doctor. A pink cannula was preferred for blood collection to ensure that the participants were not exposed to injection in every application and provided comfort and convenience. Veins located in the antecubital fossa (vena basilica, vena cephalica) were preferred because less pain remains in the arm, and they have large vessel diameters. The blood collection process was studied in accordance with asepsis and antisepsis prevention, three cc of blood was taken from the cannula in each application and transferred to purple capped EDTA (Ethylenediaminetetra-acetate) tubes. These tubes were kept in a cool place, and after the last blood was taken, they were taken to the laboratory where the analysis would be done. Blood samples collected in purple-capped tubes were centrifuged at 5000 RPM for 10 min in the laboratory and portioned after separating the plasma and stored at -80 C. After the data of all participants were completed, the plasma ghrelin level was analyzed by the ELISA method with the Affymetrix eBioscience brand kit.

Statistical Analysis: The analysis of the data was done in SPSS (IBM SPSS Statistics 23.0. Armonk, NY, USA Corp; 2013) for Windows 15 package program. In this study, it was hypothesized that there is an association between acute saccharin consumption and both ghrelin secretion and appetite.

The area under the curve of the blood ghrelin and VAS scores of the individuals was calculated using Microsoft Office Excel 2013 package program. The mean ($\bar{X}$) and standard deviation (SD), and min-max values were shown for dependent variables with a normal distribution. Nominal variables were given as number and percentage (%).

The regularity of the distribution for each parameter was evaluated using the Shapiro–Wilk test, and it was determined that the data showed normal distribution. The comparison among trials was performed using the Repeated Measures ANOVA test for the specified variables. Bonferroni correction was applied to find the difference between binary groups. Interim analysis was not done; statistical analysis was made in the period following the collection of data. The results were considered statistically significant at the $p<0.05$ level.

RESULTS

A total of 9 male volunteers with a mean age of 23.6±3.17 years participated in the study. The participants' mean body mass index value was 21.4±1.73 kg/m^2, and the body fat ratio was varied between 5.5-18.7% (Table 1).

Table 1. Mean and standard deviation values of age, body mass index, body analysis and physical activity levels of the participants (n=9)

Characteristics (n:9)	**X̄±SD**	**Min-Max**
Age (years)	23.6±3.17	20-29
BMI (kg/m^2)	21.4±1.73	19.1-24.1
Body fat ratio (%)	12.2±4.68	5.5-18.7
Muscle mass (kg)	54.3±3.88	49.1-60.7
Visceral fat level	1.7±1.06	1-3.5
Physical activity level	1.5±0.12	1.37-1.69

There was no statistically significant difference in serum ghrelin levels at the beginning and 30th min after consuming test drinks (p>0.05). After the consumption of test drink containing water and saccharin, the mean ghrelin level was higher at 60th and 120th than sucrose test drink consumption (p<0.05). In addition, the mean ghrelin level at 90 min following the consumption of the test drink containing saccharin was higher than the consumption of the sucrose test drink (p<0.05). The serum ghrelin level was significantly lower in the 180th min following consumption of the sucrose-containing test drink compared to water consumption (p<0.05) (Table 2).

Table 2. Mean and standard deviation values of serum ghrelin of participants at baseline and after test drinks consumption (n=9)

Ghrelin (pg/ml) / Intervals (min)	**Test Drinks**			**p**
	Saccharin	**Water**	**Sucrose**	
	X̄±SD	**X̄±SD**	**X̄±SD**	
Baseline	2249.4±1318.40	2205.0±1140.88	2230.0±1138.08	0.87
30	2289.5±1287.31	2273.8±1198.56	1851.7±1087.48	0.05
60	2424.8±1317.18^{a}	2356.8±1258.02^{a}	1493.2±891.89^{b}	0.001*
90	2291.9±1246.59^{a}	2136.7±1261.10^{ab}	1405.1±938.12^{b}	0.001*
120	1779.2±1013.06^{a}	1756.5±1156.13^{a}	1105.6±670.07^{b}	0.003*
180	1561.5±942.81^{ac}	1539.8±954.62^{ab}	1115.5±685.01^{c}	0.01*
p	0.003*	0.001*	0.0002*	

*Repeated Measures ANOVA Test *p<0.05*

^{abc} *Statistically significant difference between interventions*

For mean serum ghrelin, at the 60th and 120th minutes, sucrose was different from the others, at the 90th-minute saccharin and sucrose were different, and at the 180th minute, water and sucrose were different.

For saccharin trial, mean serum ghrelin was different at 90th minute from at 120th and 180th minutes. For water trial, mean serum ghrelin was different at 180th minute from at 30th and 60th minutes. For sucrose trial, mean serum ghrelin was different at baseline from at 60th, 120th, and 180th minutes. mean serum ghrelin was different at 30th minute from at 120th minute.

When the serum ghrelin responses of individuals were examined after consumption of test drink, ghrelin release after consumption of saccharin and water was higher than ghrelin release after sucrose consumption during the study (p<0.05). No statistically significant difference was found between the effects of saccharin and water consumption on the ghrelin response (p>0.05) (Table 3).

Table 3. Serum ghrelin responses of participants at baseline and after test drinks consumption (n=9)

Area under the curve (AUC) for ghrelin (pg/dlxmin)	**Test Drinks**			**p**
	Saccharin	**Water**	**Sucrose**	
	X̄±SD	**X̄±SD**	**X̄±SD**	
0-120 min	270615.5±148274.29^{ab}	262530.2±14334.50^{b}	192532.0±111356.99^{c}	0.002*
120-180 min	50110.8±28763.34^{ab}	49443.3±31560.30^{b}	33316.5±20175.86^{c}	0.014*
0-180 min	320726.3±175719.31^{ab}	311973.5±173046.54^{b}	225848.5±131022.54^{c}	0.002*
p	0.001*			

*Repeated Measures ANOVA Test *p<0.05*

^{abc} *Statistically significant difference between interventions*

For mean serum ghrelin responses, sucrose was different from the others.

For all trials, there were differences between AUCs.

As a result of the appetite scale applied after consuming the test drinks, the mean desire to eat and the prospective food consumption of the participants at the 120th min were found to be statistically significantly higher in saccharin application than sucrose application (p<0.05). It was determined that the mean scores obtained from other parameters of the appetite scale did not differ (p>0.05) (Figure 2).

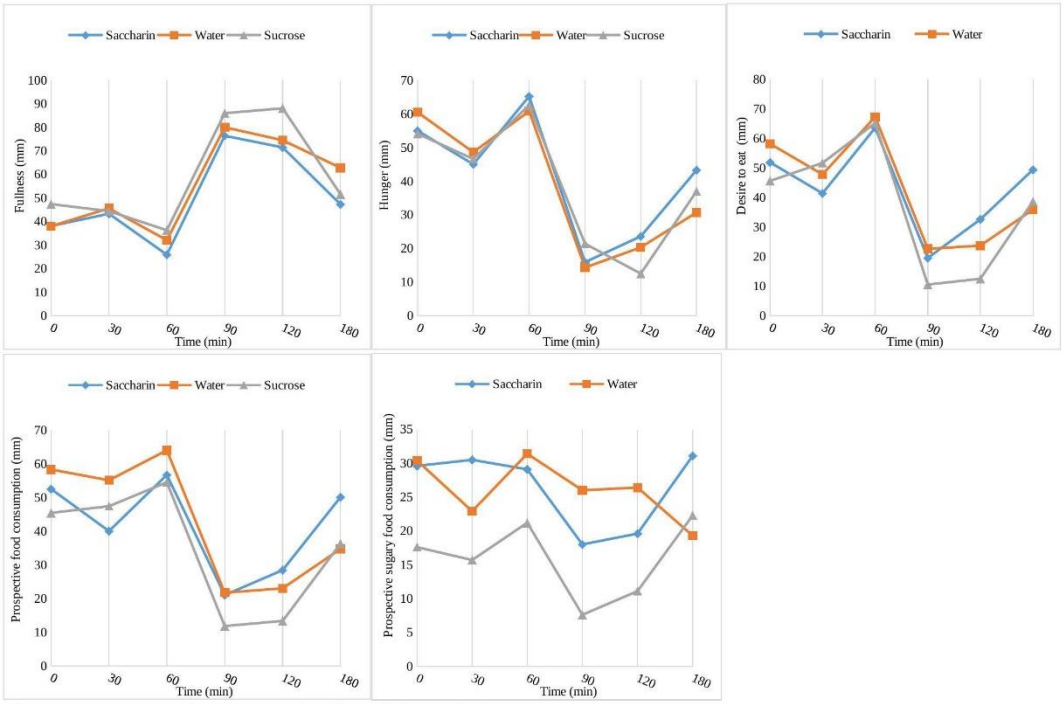

Figure 2. Appetite status of participants at baseline and after test drinks consumption

After the application ended, when the food consumption record data recorded by the participants until the end of the day were evaluated, no significant difference was found between the groups in terms of mean energy, macronutrients, and fiber intake (p>0.05) (Table 4).

Table 4. Energy and nutrient intakes of the participants on the test day

Energy and Nutrients	Test Drinks			p
	Saccharin	Water	Sucrose	
	X̄±SD	X̄±SD	X̄±SD	
Energy (kcal)	1602.7±477.96	1676.7±647.88	1334.5±403.21	0.12
Carbohydrate (g)	203.0±73.10	219.1±106.53	142.1±32.94	0.06
Protein (g)	51.9±17.34	61.7±28.22	48.9±12.53	0.31
Fat (g)	62.8±21.58	59.4±23.49	62.5±27.83	0.92
Dietary fiber (g)	18.0±11.59	21.5±16.74	12.9±6.44	0.14

*Repeated Measures ANOVA Test *p<0.05*
[abc] Statistically significant difference between interventions
There was no difference between values.
The breakfast meal consumed between 09:00 and 12:00 in the morning, which was the application period, was not included.

DISCUSSION

Appetite, which has a very complex mechanism, is controlled by neural and hormonal systems, and many factors affect it. The main hormone known to be associated with appetite is ghrelin (21). While the preprandial level of ghrelin depends on the activation of the autonomic nervous system (22), the decrease in the postprandial level depends on the macronutrient content of the meal (23). Because there is evidence that the subunits of taste receptors are located on ghrelin cells, but the mechanism is not fully known (24). In addition, simple sugars, it is known that artificial sweeteners also activate sweet taste receptor (25). The fact that artificial sweeteners used to restrict energy intake and provide sweet taste has this effect, suggesting that if artificial sweeteners are consumed in the meal, it may affect the next preprandial ghrelin levels and, therefore the appetite level. While this effect was found in some animal studies (26, 27), no such effect was found in others (28, 29). In this study, in which the effect of saccharin on appetite was examined, the strength of desire to eat and the prospective food consumption score after the 120th min after consumption of saccharin were found to be higher compared to sucrose consumption (p<0.05) (Figure 2). In the Visual Analogue Scale (VAS) score application, the scores of the expressions with the potential to increase energy intake such as hunger, prospective food consumption, and prospective sugary food consumption were higher in saccharin application. However, when the energy, macronutrients, and fiber intakes were compared after the applications, no significant difference was found (p>0.05) (Table

4). This result suggests that saccharin may have an acute effect on appetite. However, it should be considered that this effect on appetite may continue in case of continuous saccharin consumption. In a study conducted with 30 healthy male individuals comparing the effects of test drinks containing aspartame, monk fruit, stevia, and sucrose, there was no difference between the daily total energy intake of individuals consuming a drink containing sweetener and the daily total energy intake of individuals consuming a drink containing sucrose. However, it was determined that individuals who consume beverages containing sweeteners have higher energy intake at the next meal than the other group (6). In a study in which the effect of consumption of a diet drink sweetened with aspartame and a standard beverage was compared with healthy adult males and females, the total energy intake was similar (30). In another study, the effects of aspartame, monk fruit, stevia, and sucrose, which have the same sweetness ratio, on energy intake in 10 healthy male individuals were examined, and it was reported that the energy intake of those consuming non-energy sweeteners was higher than natural sweeteners and sucrose (5). It was first suggested in the aspartame study published in 1986 that the consumption of non-energy sweeteners increased appetite, and it was reported that aspartame beverage causes more hunger than water or glucose-containing drink (31). In a study by Rogers et al. (1988) on the appetite and nutritional intake of saccharin, aspartame, acesulfame-K and glucose and water with an equally sweet taste, participants were given a test meal one hour after the consumption of the test drink. As a result, it was stated that sweetener consumption stimulated hunger, and especially aspartame significantly increased the desire to eat (16). These data support the view that artificial sweeteners can increase energy intake and cause weight gain by changing appetite (5, 13, 14). Besides, in a study in which 1453 adults were followed for 28 years between 1984 and 2012, it was found that there was a relationship between long-term use of low-energy sweeteners and the prevalence of obesity and type 2 diabetes (14). Although different types and doses of artificial sweeteners used in studies cause contradictory results, artificial sweeteners such as saccharin, aspartame, acesulfame-K, and sucralose are thought to increase appetite.

This effect of artificial sweeteners on appetite may be due to their ability to increase orexigenic hormone levels. Therefore, the effect of saccharin on the ghrelin level was also examined, and it was found that the mean ghrelin level was higher at the 60th, 90th, and 120th min following the consumption of the test drink containing saccharin compared to the consumption of the sucrose test drink ($p<0.05$) (Table 2). In other words, ghrelin releases after consumption of saccharin and water during the study were higher compared to ghrelin release after sucrose consumption ($p<0.05$) (Table 3). This result shows that saccharin can affect appetite by increasing the blood ghrelin level. There is no study investigating the effect of saccharin on the ghrelin level in the literature, but the results of studies conducted with other sweeteners support the results of this study (14-16). In the study of Brown et al. (2011) comparing the effect of sucrose and sucralose, it was stated that sucrose provided a moderate decrease in acylated ghrelin level and sucralose did not have this effect. Based on this result, the researchers stated that nondecreasing the ghrelin level may increase energy intake (18).

From another point of view, the increase in ghrelin level after saccharin consumption may not only increase the appetite but also increase the desire to consume saccharin or sugar-containing foods and beverages. This view is supported by the study showing that intraperitoneally injected ghrelin in mice increases the consumption of food containing saccharin and that the increase in ghrelin level causes an increase in consumption of sweet-tasting food regardless of energy content (15). Excessive food consumption caused by sweet and tasty flavors may be due to decreased activation of orexigenic neuropeptides and the opioid system (32).

It is also suggested that artificial sweeteners affect not only ghrelin but also other hormone levels that affect appetite (4, 15, 29). It is important and necessary to evaluate orexigenic and anorexigenic hormones together to explain the effect of saccharin on appetite more clearly.

Among the strengths of the study was that the study results suggested that artificial sweeteners like saccharine, known to be completely ineffective, may be particularly effective on appetite. Also, standard breakfast was given to prevent long-time hunger and only males were included to avoid various influences on data of the study. One of the limitations of the study was that it was to determine the sample size at a minimal level because the study included invasive interventions. In addition, ad libitum meals could have been given after trials so that a comparison of daily energy and nutrient intakes could have been made. Thus, it could have been tested whether there was a difference between the energy and nutrients taken in the acute period. These are among the limitations of this research.

CONCLUSION

In this study, it was determined that saccharin increased ghrelin release from the 60th min, and also increased the desire to eat at the 120th min and the food consumption potential in healthy and normal-weight adult males. It is important to evaluate this effect of saccharin in individuals with different health problems such as obesity, metabolic syndrome, or diabetes, and in individuals of

different ages and genders. Besides, the acute effect of saccharin was investigated in this study. Longitudinal studies including other parameters affecting the appetite are needed to reveal the effects of saccharin on appetite metabolism more clearly.

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Conflict of Interest: The authors declare that they have no conflicts of interest.

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CASE REPORT

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Paraneoplastic Severe Sensorimotor Axonal Polyneuropathy in Pancreatic Neuroendocrine Carcinoma: A Case Report and Review of the Literature

ABSTRACT

Objective: Paraneoplastic neurological syndromes (PNSs) are a diverse group of neurological disorders affecting any part of the nervous system before or during cancer.

Case: A 78-year-old man first experienced pain and burning in the upper extremity three years previously, to which muscle weakness was added a short time later. The same symptoms developed in the lower extremities one year previously. He was admitted to the intensive care unit due to pneumonia and was conscious but quadriplegic with a modified Rankin score of 5. Abdominal computed tomography showed mass lesions in the liver and pancreas. Biopsies revealed pancreatic small cell neuroendocrine carcinoma. Electrophysiological studies revealed severe sensorimotor axonal polyneuropathy. Paraneoplastic sensorimotor axonal polyneuropathy was diagnosed since other causes of polyneuropathy had been excluded. Palliative care was considered due to the patient's poor functional state.

Conclusions: Early diagnosis of cancer is of paramount importance in patients with PNSs if appropriate treatment is to be provided.

Keywords: Neuroendocrine Carcinoma, Quadriplegia, Ki67, Paraneoplastic Neurological Syndromes.

Pankreatik Nöroendokrin Karsinomda Paraneoplastik Ciddi Sensorimotor Aksonal Polinöropati: Vaka Sunumu ve Literatür Taraması

ÖZET

Amaç: Paraneoplastik nörolojik sendromlar (PNSs), kanser öncesi veya kanser sırasında gelişen, sinir sisteminin herhangi bir kısmını etkileyen çeşitli nörolojik hastalıkları içermektedir.

Vaka: Yetmiş sekiz yaşında erkek hastanın üç yıl önce üst ekstremitelerde ağrı ve yanma hissi şikayetleri başlamış ve kısa süre sonra kas güçsüzlüğü eklenmiş. Bir yıl önce de alt ekstremitelerde benzer şikayetler ortaya çıkmış. Yoğun bakım ünitesine pnömoni tansıyla yatırılan hastanın yatış esnasında bilinci açık, fakat kuadriplejik ve modifiye Rankin skoru 5 idi. Abdomen bilgisayarlı tomografi karaciğer ve pankreasta kitle lezyonlarının olduğunu gösterdi. Lezyonyonlardan alınan biyopsiler pankreas orjinli küçük hücreli nöroendokrin karsinom olarak raporlandı. Elektrofizyolojik testler ciddi sensorimotor aksonal polinöropati ile uyumluluk gösteriyordu Diğer polinöropati nedenleri dışlandıktan sonra, hastaya paraneoplastik sensorimotor aksonal polinöropati tanısı konuldu. Hastanın fonksiyonel kapasitesi düşük olduğundan palyatif tedavi planlandı.

Sonuç: PNS'li hastalarda uygun tedavinin başlanması için erken kanser tanısının konulması önem arz etmektedir.

Anahtar Kelimeler: Nöroendokrin Karsinom, Kuadripleji, Ki67, Paraneoplastik Nörolojik Sendromlar.

INTRODUCTION

Paraneoplastic neurological syndromes (PNSs) include a heterogeneous group of disorders developing prior or during cancer due to remote effects of the tumor on the nervous system, but are not related to tumor infiltration, chemotherapy, or metastasis (1,2). PNSs are seen in less than 1% of patients with cancer (3). The expression of various neuronal proteins by cancer cells triggers an immune response misdirected to the nervous system (3). PNSs can affect the central, peripheral, or autonomic nervous systems. Although lung cancer is commonly encountered in patients with PNSs, many cancers within the body can lead to immunological reactions against the nervous system (2,3). Other etiologies of neurological disorders should be ruled out before diagnosis of PNSs, such as nutritional deficiency, vascular insults, infections, toxic substance exposures, medication side-effects, and metabolic derangement (2).

Neuroendocrine neoplasms (NENs) are uncommon, but can occur in various parts of the body, such as the lung, small intestine, stomach, pancreas, large intestine, central nervous system, and thymus (4,5). NENs from the bronchopulmonary and gastroenteropancreatic organs account for over 90% of all cases (4). More than half of extrapulmonary NENs occur in the digestive tract. NENs consist of two families, well-differentiated (low-grade to intermediate-grade) NENs, known as neuroendocrine tumors, and poorly differentiated (high grade) NENs, known as neuroendocrine carcinomas (NECs). Since most gastroenteropancreatic NECs are clinically silent, early detection is difficult. Metastatic disease at diagnosis is reported in 50% to 70% of patients (5). We describe a patient with quadriplegia who was admitted to the intensive care unit (ICU) due to respiratory failure and diagnosed with paraneoplastic sensorimotor axonal polyneuropathy in association with metastatic pancreatic small cell NEC.

CASE REPORT

A 78-year-old man was admitted to the hospital due to cough and sputum persisting for 10 days. The patient was intubated 24 hours subsequently due to respiratory failure and was admitted to the ICU. His history revealed a percutaneous coronary intervention 10 years previously, right and left carpal tunnel release operations two years previously, and a diagnosis of axonal polyneuropathy one year previously. He first experienced pain and burning in the upper extremities approximately three years previously, with muscle weakness being added to the symptoms shortly thereafter. The same symptoms developed in the lower extremities one year previously. The symptoms, especially muscle weakness, were progressive, and the patient had become dependent in daily living. He had been unable to walk without assistance for the previous six months and became completely bedridden in the preceding week. He had not benefited from the right and left carpal tunnel release surgeries, vitamin medications, or physiotherapy. In the ICU, he was conscious but was unable to move any of his extremities. His modified Rankin score (mRS) was 5 with no deep tendon reflexes. There were no signs of facial asymmetry or local neurological abnormalities. His leukocyte count and C-reactive protein level were $21.1x10^9$/L (normal, $4\text{-}12x10^9$/L) and 2.8 mg/dL (normal, <0.5 mg/dL), respectively. Other laboratory test results including hemoglobin, platelet, vitamin B12, folic acid, hemoglobin A1c, liver and kidney function tests, and thyroid hormone levels were within normal limits. Human immunodeficiency virus, hepatitis virus C and B, severe acute respiratory syndrome coronavirus-2, protein electrophoresis, and blood smear studies were unremarkable. Cranial and lumbar magnetic resonance imaging (MRI) was normal. Chest computed tomography (CT) showed right lung pneumonia with no mass lesion. Abdominal CT showed three lesions in the liver, 11x9.2 cm, 3.3x3.2 cm, and 2.1x2 cm in size (Fig. 1a). A 2.6x2.4 cm lesion of a cystic nature was noted in the head of the pancreas (Fig. 1b).

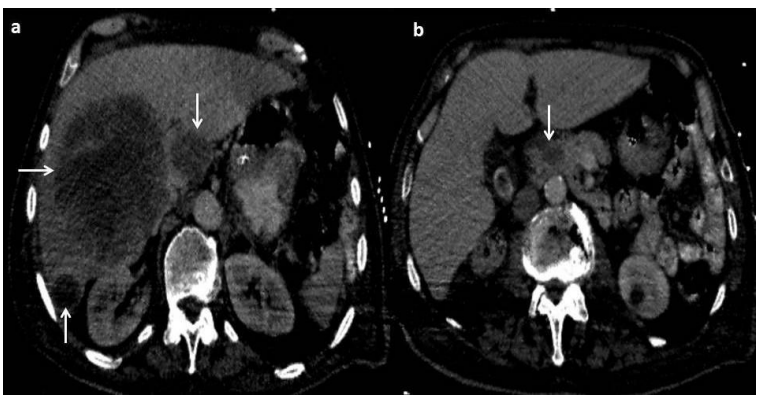

Figure 1. Abdominal CT showing three metastatic lesions in the liver (a, white arrows), and a lesion of a cystic nature in the head of the pancreas (b, white arrow).

Upper and lower gastrointestinal endoscopies and testicular ultrasonography were normal. CT guided-pancreas and ultrasonography guided-liver biopsies showed that the tumor tissues were composed of cells arranged in irregular cords and nest-like groups with scant cytoplasm, and finely dark and granular chromatin (Fig. 2a). Nuclear molding and focal necrosis were observed. The tumor exhibited strong positivity with chromogranin A and CD56 (Fig. 2b, Fig. 2c). The Ki-67 proliferation index was greater than 55% (Fig. 2d).

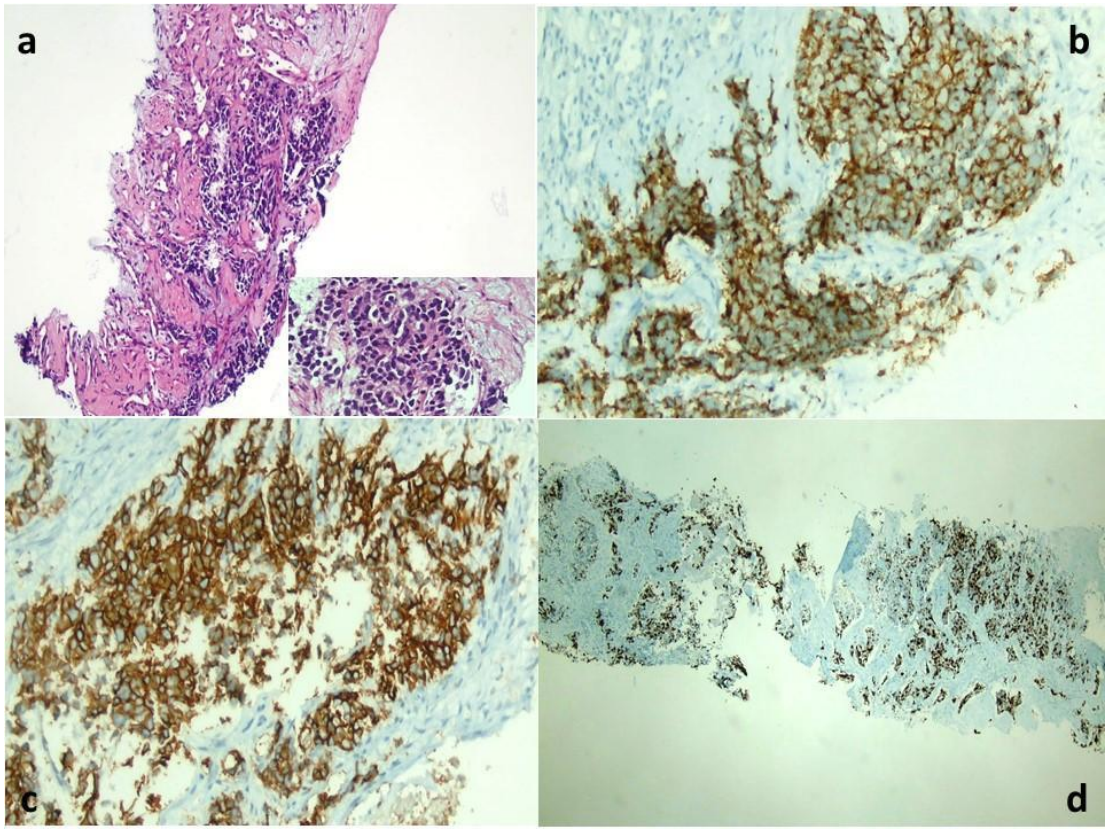

Figure 2. The tumor was composed of cells arranged in irregular cords and nest-like groups (x10), and cells with scant cytoplasm, and finely dark and granular chromatin are shown in the insert photo (x40) (a). Tumor cells exhibiting chromogranin A (b) and CD56 positivity (x20) (c), with a Ki67 proliferation index > 55% (x10) (d).

The patient was diagnosed with pancreatic small cell type neuroendocrine carcinoma. Electrodiagnostic studies were performed to examine the motor and sensory nerves of the bilateral lower extremities and the right-side upper extremity. Electromyography indicated that sensory nerve action potentials were not detected in either of the lower limbs or the right upper extremity. Motor nerve conduction study showed decreased amplitude and conduction velocity, and prolonged latency. Needle electromyography revealed reduced recruitment of the distal muscles and denervation. The patient was diagnosed with peripheral sensorimotor, dominantly axonal and particularly demiyelinating, polyneuropathy on the basis of the electromyography findings. Paraneoplastic sensory motor polyneuropathy was diagnosed since other causes of polyneuropathy had been excluded. Antineuronal antibodies (anti-Hu, -Ri, -Yo, -Ma2, -amphiphysin and -CV2) were negative. The patient was weaned from mechanical ventilation and transferred to the inpatient clinic. Palliative therapy was considered due to the patient's poor performance status, but he died one month later.

DISCUSSION

PNSs include a diverse group of disorders affecting any part of the nervous system. Although many types of tumor are reported to be associated with PNSs, lung, ovarian and breast cancers are the most commonly encountered forms in previous studies (6-9). The symptoms of PNSs precede the tumor symptoms in the majority of patients, ranging from 68% to 85% (6-8). Tumor metastasis at the time of diagnosis occurs in 21% of patients with malignancy (6). A workup for paraneoplastic etiology is therefore recommended in patients in whom other causes of neuropathy have been eliminated. Multimodality imaging including CT, MRI, ultrasonography, and endoscopy may be required to diagnose a tumor. Fluorodeoxyglucose positron emission tomography scanning is even required to detect an occult malignancy which is not observed with conventional imaging (7).

The presence of antineuronal antibodies in both the diagnosis of PNSs and for directing the investigation of underlying malignancy is well established in a wide range of patients, between 28% and 77%, and small cell lung cancer (SCLC), thymoma, ovarian cancer, melanoma and breast cancer are generally shown to be associated with these antibodies (2,7,9). Although there are many types of antibody, the best characterized antineuronal antibodies are anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2, and anti-amphiphysin (2). However, the absence of these antibodies does not exclude a paraneoplastic syndrome (9). PNSs can present clinically as acute, subacute or chronic, and may progress, if not treated, concluding in high functional disability (7). The prognosis depends on tumor treatments (surgery, radiotherapy, and chemotherapy) which stabilize or improve the neurological symptoms, and tumors remain the primary cause of death in these patients (6,7). Early diagnosis, mRS <3, and absence of metastasis are good prognostic factors (6). In the present case, a sensorimotor axonal polyneuropathy associated with an identified metastatic cancer was diagnosed and other causes of polyneuropathy were excluded. The patient's symptoms were progressive, resulting in a mRS of 5.

Gastropancreatic NECs are high-grade (poorly differentiated) carcinomas, the counterparts of SCLC or large-cell neuroendocrine carcinomas of the lung with a high proliferative index (Ki-67 >20%), and thus more aggressive and fatal (4,5,10). They are histologically classified as small or large cell cancers, small cell cases having a poorer prognosis than large cell cases (10). The presence of necrotic areas in the tumor is a sign of a rapidly growing cancer and aggressive behavior. Lymph node involvement, diffuse liver metastasis, bone metastasis, tumor histology (small cell), poor performance status, and a high proliferative index are the most important poor prognostic factors in these patients (10-12). A large retrospective study by Sorbye et al. showed that patients with Ki-67 ≥55% had poorer prognosis than those with Ki-67 <55% (12). Median survival was 38 months for patients with localized disease, 16 months for patients with regional disease, and five months for patients with distant disease (5). A study including only pancreatic NECs reported median survival of 9.1 months, with a one-year survival rate of 34% (11). Unfortunately, median survival is only one month without chemotherapy in patients with advanced gastropancreatic NECs (12). Rapid referral to an oncologist is therefore of paramount importance. Therapeutic strategies are generally extrapolated from the treatment regimens for SCLC. The patient described in the present case had advanced disease with a poor functional state and high mitotic rate, was unable to receive chemotherapy, and died in one month after the cancer diagnosis.

PNSs are rare but important clinical conditions that often precede the diagnosis of cancers. Prompt recognition leads to tumor discovery at an earlier and curable stage. The investigation of antineuronal antibodies is useful in identifying these conditions, but negative test results do not exclude PNSs. As long-term outcomes are mainly dependent on tumor progression and its complications, early diagnosis and treatment of cancers are of paramount importance.

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